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Lewis J. Kreisler
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Date: DECEMBER 8, 1999

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PATENT APPLICATION

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re application of:

William Harris, et al.

Group No.: 1614

Serial No.: 09/422,451

Filed: October 21, 1999

For: **BICYCLIC NITROGEN HETEROCYCLES**

TRANSMITTAL OF CERTIFIED COPIES

December 8, 1999

Assistant Commissioner for Patents
Washington, D.C. 20231

Dear Sir:

Attached please find the certified copies of the foreign applications from which priority is claimed for this case:

Country	Application No.	Filing Date
Great Britain	9823277.0	October 23, 1998
Great Britain	9920044.6	August 24, 1999

Respectfully submitted,

Lewis J. Kreisler
Attorney for Applicant
Reg. No. 38522
Hoffmann-La Roche Inc.
340 Kingsland Street
Nutley, New Jersey 07110
Phone: (973) 235-4387

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1/77

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The Patent Office

Cardiff Road
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1. Your reference

P20174GB: SDV

2. Patent application number
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23 OCT 1998

9823277.0

3. Full name, address and postcode of the or of each applicant *(underline all surnames)*

F. HOFFMANN-LA ROCHE AG.
124 GRENZACHERSTRASSE,
CH-4070 BASLE,
SWITZERLAND

4200040 02

Patents ADP number *(if you know it)*

If the applicant is a corporate body, give the country/state of its incorporation

SWITZERLAND

4. Title of the invention

BICYCLIC NITROGEN HETEROCYCLES.

5. Name of your agent *(if you have one)*

~~**Carpmaels & Ransford**~~ Forrester Ketley + Co

"Address for service" in the United Kingdom to which all correspondence should be sent *(including the postcode)*

~~**43 Bloomsbury Square**~~
~~**London.**~~
~~**WC1A 2RA**~~

Forrester House
52 Bounds Green Road
London
N11 2EY

See 6/77 MS 14/99.

Patents ADP number *(if you know it)*

~~**83001**~~ 133001

6. If you are declaring priority from one or more earlier patent applications, give the country and the date of filing of the or of each of these earlier applications and *(if you know it)* the or each application number

Country	Priority application number *(if you know it)*	Date of filing *(day / month / year)*

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Number of earlier application	Date of filing *(day / month / year)*

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Patents Form 1/77

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Continuation sheets of this form	
Description	**52**
Claim(s)	**4**
Abstract	**1**
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Priority documents	
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Statement of inventorship and right to grant of a patent *(Patents Form 7/77)*	
Request for preliminary examination and search *(Patents Form 9/77)*	
Request for substantive examination *(Patents Form 10/77)*	
Any other documents *(please specify)*	

11. I/We request the grant of a patent on the basis of this application.

Signature Date

Carpmaels & Ransford **23rd October 1998**

12. Name and daytime telephone number of person to contact in the United Kingdom

MR. S.D. VOTIER **0171 242 8692**

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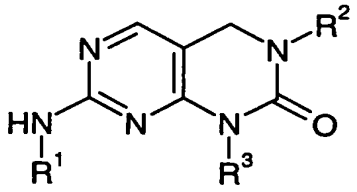
Ref. 20'232

Bicyclic nitrogen heterocycles

The present invention relates to bicyclic nitrogen heterocycles. More particularly, the invention is concerned with amino-substituted dihydropyrimido[4,5-d]pyrimidinone derivatives, a process for their manufacture and pharmaceutical preparations containing them.

The amino-substituted dihydropyrimido[4,5-d]pyrimidinone derivatives provided by the present invention are compounds of the general formula



(I)

wherein

R^1 represents hydrogen, lower alkyl, aryl, aryl-lower alkyl, heteroaryl, heteroaryl-lower alkyl, lower cycloalkyl or lower cycloalkyl-lower alkyl,

R^2 represents lower alkyl, aryl, aryl-lower alkyl, heteroaryl, heteroaryl-lower alkyl, lower cycloalkyl or lower cycloalkyl-lower alkyl, and

R^3 represents hydrogen, lower alkyl, aryl, aryl-lower alkyl, heteroaryl, heteroaryl-lower alkyl, lower cycloalkyl, lower cycloalkenyl or lower cycloalkyl-lower alkyl,

and pharmaceutically acceptable salts of basic compounds of formula I with acids.

The compounds of formula I and their aforementioned salts are inhibitors of protein kinases, especially of the T-cell tyrosine kinase $p56^{lck}$. They can accordingly be used in the treatment or prophylaxis of inflammatory, immunological, oncological, bronchopulmonary, dermatological and cardiovascular disorders, in the treatment of asthma, central nervous system disorders or diabetic complications or for the prevention of graft rejection following transplant surgery.

As used herein, the term "lower alkyl", alone or in combination as in "aryl-lower alkyl", "heteroaryl-lower alkyl" and "lower cycloalkyl-lower alkyl", means a straight-chain or branched-chain alkyl group containing from 1 to 7, preferably from 1 to 4, carbon atoms, such as methyl, ethyl, n-propyl, isopropyl, n-butyl, sec.butyl, tert.butyl, n-pentyl, n-hexyl, n-heptyl and the like.

The term "lower alkoxy" means a lower alkyl group as defined earlier which is bonded via an oxygen atom, with examples of lower alkoxy groups being methoxy, ethoxy, n-propoxy, isopropoxy, n-butoxy, sec.butoxy, tert.butoxy, n-pentoxy and the like.

The term "lower cycloalkyl", alone or in combination as in "lower cycloalkyl-lower alkyl", means a cycloalkyl group containing from 3 to 7, preferably from 4 to 6, carbon atoms, i.e. cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl or cycloheptyl.

The term "lower cycloalkenyl" means a cycloalkenyl group containing from 4 to 7 carbon atoms, e.g. cyclobutenyl, cyclopentenyl, cyclohexenyl and the like.

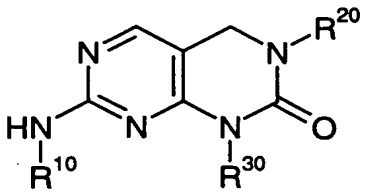
The term "aryl", alone or in combination as in "aryl-lower alkyl", means a phenyl or naphthyl group which is optionally mono- or multiply-substituted by halogen, lower alkyl, lower alkoxy, trifluoromethyl, hydroxy, nitro, amino, phenyl or the like or by a group of the formula -Z-NR^4R^5 or -Z-OH in which Z represents a spacer group and R^4 and R^5 each individually represent hydrogen or lower alkyl or R^4 and R^5 together with the nitrogen atom to which they are attached represent a 4-, 5- or 6-membered saturated or partially unsaturated or 5- or 6-membered aromatic heterocyclic group which contains one or more hetero atoms selected from nitrogen, sulphur and oxygen and which is optionally substituted by lower alkyl, lower alkoxy and/or oxo and/or which is optionally benz-fused. Examples of spacer groups are -$(CH_2)_m$- in which m stands for 1, 2, 3 or 4 and -$O(CH_2)_n$- in which n stands for 2, 3 or 4. Pyrrolidinyl, piperidinyl, piperazinyl, morpholinyl and indolyl are examples of heterocyclyl groups formed by R^4 and R^5 together with the nitrogen atom to which they are attached. Thus, the term "aryl" embraces groups such as phenyl, 1-naphthyl, 2-hydroxyphenyl, 3-bromophenyl, 4-methoxyphenyl, 2,6-difluorophenyl, 2,6-dichlorophenyl, 3-(2-aminoethyl)-phenyl, 4-(2-hydroxyethyl)-phenyl, 4-(2-diethylamino-ethoxy)-phenyl, 3-(2-phthalimidoethyl)-phenyl and the like.

The term "heteroaryl", alone or in combination as in" heteroaryl-lower alkyl", means a 5- or 6-membered heteroaromatic group which contains one or more hetero

atoms selected from N, S and O and which may be benz-fused and/or substituted in the same manner as "aryl" defined earlier. Examples of typical heteroaryl groups are thienyl, furyl, pyridyl, pyrimidinyl, quinolyl, indolyl, benzofuranyl and the like.

The term "halogen" means fluorine, chlorine, bromine or iodine.

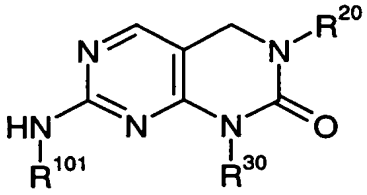
A preferred class of compounds provided by the present invention comprises those of the general formula



(Ia)

wherein R^{10} represents lower alkyl, aryl or aryl-lower alkyl, R^{20} represents aryl and R^{30} represents hydrogen, lower alkyl, aryl or aryl-lower alkyl.

Preferred compounds falling under formula Ia have the formula



(Iai)

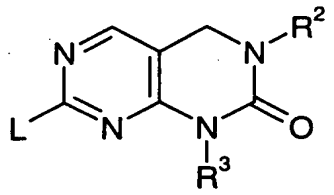
wherein R^{101} represents aryl and R^{20} and R^{30} have the significance given earlier.

R^{101} preferably represents phenyl. R^{20} preferably represents halophenyl, especially 2,6-dichlorophenyl. R^{30} preferably represents phenyl substituted by a group of the formula $-Z-NR^4R^5$ defined hereinbefore.

1-[3-(2-Aminoethyl)phenyl]-7-anilino-3-(2,6-dichlorophenyl)-3,4-dihydro-pyrimido[4,5-d]pyrimidin-2(1H)-one is a particularly preferred compound of formula I.

According to the process provided by the present invention, the aforementioned amino-substituted dihydropyrimido[4,5-d]pyrimidinone derivatives are manufactured by

(a) reacting a compound of the general formula



(II)

wherein R^2 and R^3 have the significance given earlier with the proviso that any hydroxy or amino group present may be in protected form, and L signifies lower alkylthio or lower alkanesulphonyl,

with an amine of the general formula

$$R^1—NH_2 \qquad \text{(III)}$$

wherein R^1 has the significance given earlier, with the proviso that any hydroxy or amino group present may be in protected form,

and, where required, converting a protected hydroxy or protected amino group present in the reaction product into a free hydroxy or free amino group,

or

b) for the manufacture of a compound of formula I in which R^1 represents hydrogen, cleaving off the aryl-methyl group from a compound of formula I in which R^1 signifies aryl-methyl, and

c) if desired, converting a basic compound of formula I obtained into a pharmaceutically acceptable salt with an acid.

A protected hydroxy or protected amino group present in a starting material of formula II or III, i.e. on an aryl or heteroaryl substituent R^1, R^2 and/or R^3, can be any conventional protected hydroxy or protected amino group. Thus, for example, a hydroxy group can be protected in the form of an ether, e.g. the methyl ether, or an ester, e.g. the ethyl ester. With respect to protected amino, phthalimido is an example of such a group.

The reaction of a compound of formula II with an amine of formula III in accordance with embodiment (a) of the process can be carried out in the presence or absence of a solvent. When a solvent is used, this can conveniently be a halogenated aliphatic hydrocarbon, e.g. dichloromethane or 1,2-dichloroethane, an open-chain ether,

e.g. diethyl ether or diisopropyl ether, a cyclic ether, e.g. tetrahydrofuran, an optionally halogenated aromatic hydrocarbon, e.g. benzene, toluene, a xylene or chlorobenzene, or a formamide, e.g. dimethylformamide. Suitably, the reacton is carried out at a temperature in the range of about 0°C to about 200°C, preferably at about 100°C to about 200°C.

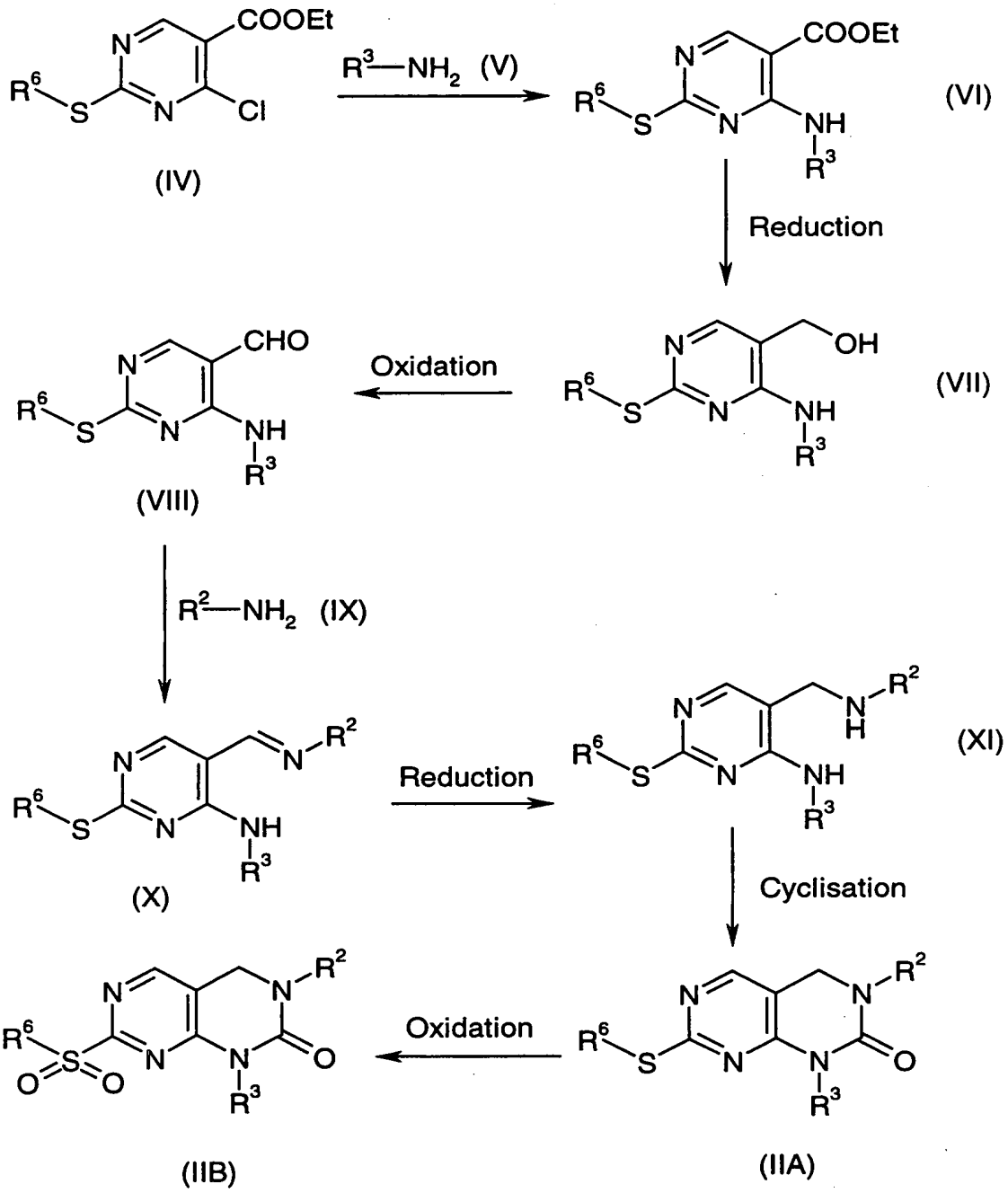
The conversion of a protected hydroxy group or a protected amino group present in a product obtained by reacting a compound of formula II with an amine of formula III can be carried out in a manner known per se. Thus, for example, an ether such as the methyl ether can be converted into hydroxy by treatment with hydrobromic acid and an ester such as the ethyl ester can be converted into hydroxy using an alkali metal aluminium hydride such as lithium aluminium hydride. Again, for example, the phthalimido group can be converted into amino by treatment with hydrazine hydrate.

The cleavage of an aryl-methyl group, e.g. lower-alkoxybenzyl such as 4-methoxy-benzyl, from a compound of formula I in which R^1 signifies aryl-methyl in accordance with embodiment (b) of the process can be carried out using methods which are known per se. For example, the cleavage can be carried out using trifluoroacetic acid, conveniently at an elevated temperature, preferably at the reflux temperature of the reaction mixture.

Compounds of formula I which are basic can form salts with inorganic acids, e.g. hydrohalic acids such as hydrochloric acid or hydrobromic acid, sulphuric acid, nitric acid or phosphoric acid, or with organic acids, e.g. formic acid, acetic acid, trifluoroacetic acid, citric acid, fumaric acid, malic acid, maleic acid, succinic acid, tartaric acid, salicylic acid, methanesulphonic acid, ethanesulphonic acid, 4-toluenesulphonic acid and the like. In accordance with embodiment (c) of the process, these salts can be formed and isolated in a manner known per se.

The starting materials of formula II are novel and also form an object of the present invention. They can be prepared as illustrated in Scheme I hereinafter in which R^2 and R^3 have the significance given earlier, subject to the foregoing proviso and R^6 represents lower alkyl.

Scheme I



Having regard to Scheme I, in the first step a compound of formula IV is reacted with a compound of formula V to give a compound of formula VI. This reaction is conveniently carried out in a solvent which is inert under the reaction conditions, preferably a halogenated aliphatic hydrocarbon, especially dichloromethane, an optionally halogenated aromatic hydrocarbon, an open-chain or cyclic ether, a formamide or a lower alkanol. Suitably, the reaction is carried out at about -20°C to about 120°C.

The next step comprises the reduction of a compound of formula VI to give an alcohol of formula VII. This reduction is carried out using lithium aluminium hydride in a manner known per se, e.g. in a solvent which is inert under the conditions of the reduction, preferably an open-chain or cyclic ether, especially tetrahydrofuran, at about -20° C to about 70°C, preferably at about 0°C to about room temperature.

Oxidation of an alcohol of formula VII in the next step yields a carboxaldehyde of formula VIII. This oxidation is carried out with manganese dioxide in a manner known per se, conveniently in a solvent which is inert under the oxidation conditions, preferably a halogenated aliphatic hydrocarbon, especially dichloromethane, or an optionally halogenated aromatic hydrocarbon. Suitably, the oxidation is carried out at about 0°C to about 60°C.

Reaction of a carboxaldehyde of formula VIII with an amine of formula IX in the next step yields a compound of formula X. This reaction may be carried out in the presence of an acid, e.g. an aromatic sulphonic acid, preferably 4-toluenesulphonic acid, with azeotropic removal of the water formed during the reaction. Conveniently, the reaction is carried out in a solvent which is inert under the reaction conditions, preferably an optionally halogenated aromatic hydrocarbon, especially toluene, and at a temperature of about 70°C to about 150°C, especially at the reflux temperature of the solvent.

The next step comprises the reduction of a compound of formula X to give a compound of formula XI. This reduction is carried out using sodium borohydride, lithium aluminium hydride or sodium triacetoxyborohydride in a manner known per se. Preferably, the compound of formula X is not purified, but rather the reaction mixture in which it is prepared is concentrated and the concentrate obtained is taken up in a solvent which is inert under the conditions of the reduction, preferably an open-chain or cyclic ether, especially tetrahydrofuran or an optionally halogenated aromatic hydrocarbon or a lower alkanol, and then treated with an aforementioned reducing agents. The reduction is suitably carried out at about 0°C to about 100°C, preferably at about 25°C

Cyclization of a compound of formula XI yields a starting material of formula IIA. This cyclisation is effected by reaction with phosgene or trichloromethyl chloroformate in a manner known per se, conveniently in the presence of a tertiary organic base, preferably a tri(lower alkyl)amine, especially triethylamine, and in a solvent which is inert under the

conditions of the reaction, preferably an open-chain or cyclic ether, especially tetrahydrofuran, an optionally halogenated aromatic hydrocarbon or a halogenated aliphatic hydrocarbon. Conveniently, the reaction is carried out at about -20°C to about 50°C, preferably at about 0°C to about room temperature.

Oxidation of a starting material of formula IIA with 3-chloroperbenzoic acid yields a starting material of formula IIB. This oxidation is carried out in a manner known per se, conveniently in a solvent which is inert under the conditions of the oxidation, preferably a halogenated aliphatic hydrocarbon, especially dichloromethane, and at about -20°C to about 50°C, preferably about 0°C to about room temperature.

Starting materials of formula IIA or IIB in which R^3 represents hydrogen can be N-substituted by treatment with an alkali metal hydride, especially sodium hydride, and subsequent reaction with a compound of the general formula

$$R^{3a}—L \qquad (XII)$$

wherein R^{3a} has any of the values accorded to R^3 hereinbefore except hydrogen, aryl or heteroaryl and L represents a leaving group.

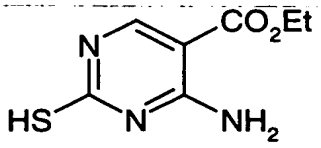
The leaving group denoted by L in a compound of formula XII can be, for example, halo, lower alkanesulphonate, e.g. methanesulphonate, trifluoromethanesulphonate or aromatic sulphonate, e.g. benzenesulphonate or 4-toluenesulphonate. L preferably represents iodo.

The N-substitution is conveniently carried out in a solvent which is inert under the reaction conditions, preferably a formamide, especially dimethylformamide, an open-chain or cyclic ether or an optionally halogenated aromatic hydrocarbon. Suitably, the reaction is carried out at about 50°C to about 200°C, preferably at about 50°C to about 150°C.

Furthermore, starting materials of formulae IIA or IIB in which R^3 signifies aryl substituted by a group of the formula $-(CH_2)_m-NR^4R^5$, wherein NR^4R^5 signifies phthalimido and m has the significance given earlier, can be prepared by cyclizing a compound of formula XI in which R^3 signifies aryl substituted by a group of the formula $-(CH_2)_m-OH$, wherein m has the significance given earlier, with phosgene and treating the reaction

product (a compound corresponding to formula IIA or IIB in which R^3 signifies aryl substituted by a group of the formula $-(CH_2)_m-Cl$, wherein m has the significance given earlier) with an alkali metal salt of phthalimide, preferably the potassium salt.

In an alternative procedure for the preparation of compounds of formula VI in Scheme I in which R^3 represents hydrogen, ethyl 4-amino-2-mercapto-pyrimidine-5-carboxylate of the formula



(XIII)

can be reacted with an iodide of the general formula

$$R^6—I \qquad \text{(XIV)}$$

wherein R^6 has the significance given earlier.

The reaction of the compound of formula XIII with an iodide of formula XIV is conveniently carried out in a solvent which is inert under the reaction conditions, preferably a ketone, especially acetone, a halogenated aliphatic hydrocarbon, an optionally halogenated aromatic hydrocarbon, an open-chain or cyclic ether or a formamide. Suitably, the reaction is effected at about -20°C to about 100°C, preferably at about 20°C

The compounds of formulae IV, V, IX, XII, XIII and XIV hereinbefore are known compounds or analogues of known compounds.

The amine starting materials of formula III hereinbefore, insofar as they are not known compounds or analogues of known compounds, can be prepared in a similar manner to the known compounds or as illustrated in the following Examples.

As mentioned earlier, the compounds of formula I and the pharmaceutically acceptable salts of basic compounds of formula I with acids are inhibitors of protein

kinases, especially of the T-cell tyrosine kinase $p56^{lck}$. This activity can be demonstrated using the following test procedure.

Reaction mixtures (25 µl) containing human recombinant $p56^{lck}$, 10 mM $MnCl_2$, 10µM ATP, 0.2 mM sodium vanadate, 20 µM peptide substrate (AlaGluGluGluIleTyr-GlyGluPheGluAlaLysLysLysLys, [γ-^{33}P] ATP (1000-2000 cpm/pmol) in 25 mM HEPES buffer (pH 7.5) and 0.1% Triton X-100 are incubated at 30°C for 60 minutes and the reaction is then stopped by the addition of 10 µl of 2% orthophosphoric acid. Radio-labelled peptide is separated from unreacted [γ-^{33}P] ATP by filtration through Millipore Multiscreen phosphocellulose cation exchange paper filters. Bound peptide is washed with 0.5% orthophosphoric acid and incorporated radioactivity is determined by scintillation spectrometry.

The degree of enzyme blockade at each concentration of test compound is calculated from the following equation:

$$\frac{\text{CPM incorporated (+ test compound + enzyme)}}{\text{CPM incorporated (- test compound + enzyme)}} \times 100$$

The IC_{50} value is that concentration of test compound which reduces by 50% the protein kinase-induced incorporation of the radiolabel under the test conditions described earlier.

1-[3-(2-Aminoethyl)phenyl]-7-anilino-3-(2,6-dichlorophenyl)-3,4-dihydro-pyrimido[4,5-d]pyrimidin-2(1H)-one has an IC_{50} of 0.03 nM in the aforementioned test.

The compounds of formula I and the pharmaceutically acceptable salts of basic compounds of formula I with acids can be used as medicaments, e.g. in the form of pharmaceutical preparations. The pharmaceutical preparations can be administered enterally, e.g. orally in the form of tablets, coated tablets, dragées, hard and soft gelatine capsules, solutions, emulsions or suspensions, nasally, e.g. in the form of nasal sprays, or rectally, e.g. in the form of suppositories. However, they may also be administered parenterally, e.g. in the form of injection solutions.

Finally, the use of compounds of formula I and their aforementioned pharmaceutically acceptable salts for the production of medicaments, especially in the treatment or prophylaxis of inflammatory, immunological, oncological, bronchopulmonary, dermatological and cardiovascular disorders, in the treatment of asthma, central nervous system disorders or diabetic complications or for the prevention of graft rejection following transplant surgery, is also an object of the invention.

The following Examples illustrate the present invention in more detail, but are not intended to limit its scope in any manner.

Example 1

A mixture of 2.55 g (6.6 mmol) of 3-(2,6-dichlorophenyl)-7-methanesulphonyl-3,4-dihydro-1-methylpyrimido[4,5-d]pyrimidin-2(1H)-one and 7 g (34 mmol) of 4-[2-(diethylamino)ethoxy]-aniline was heated at 180°C for 35 minutes and then cooled. The residue was chromatographed on silica gel using firstly 5% methanol in dichloromethane and then dichloromethane/methanol/acetic acid/water (240:24:3:2) for the elution. Product-containing fractions were combined and evaporated. The residue was evaporated with toluene and then dissolved in 150 ml of dichloromethane. The solution was washed with 100 ml of saturated aqueous sodium bicarbonate solution, dried over magnesium sulphate and evaporated to give 1.18 g (35%) of crude product. Purification by crystallization from cyclohexane/ethyl acetate gave 310 mg (9%) of pure 3-(2,6-dichlorophenyl)-7-[4-[2-(diethylamino)ethoxy]anilino]-3,4-dihydro-1-methylpyrimido[4,5-d]pyrimidin-2(1H)-one as a white solid of melting point 123-124°C.

The 3-(2,6-dichlorophenyl)-7-methanesulphonyl-3,4-dihydro-1-methylpyrimido-[4,5-d]pyrimidin-2(1H)-one used as the starting material was prepared as follows:

a) A solution of 20 g (86 mmol) of ethyl 4-chloro-2-methylthiopyrimidine-5-carboxylate in 250 ml of dichloromethane was cooled to 0°C and treated slowly with 35 ml (281 mmol) of a 33% solution of methylamine in ethanol. After stirring for 30 minutes 150 ml of water were added and the phases were separated. The organic phase was dried over magnesium sulphate and filtered. The filtrate was evaporated under reduced pressure to give 19 g (97%) of ethyl 4-methylamino-2-methylthiopyrimidine-5-carboxylate as a white solid.

The compounds of formula I and their aforementioned pharmaceutically acceptable salts can be processed with pharmaceutically inert, organic or inorganic carriers for the production of pharmaceutical preparations. Lactose, corn starch or derivatives thereof, talc, stearic acid or its salts and the like can be used, for example, as such carriers for tablets, coated tablets, dragées and hard gelatine capsules. Suitable carriers for soft gelatine capsules are, for example, vegetable oils, waxes, fats, semi-solid and liquid polyols and the like; depending on the nature of the active ingredient no carriers are, however, usually required in the case of soft gelatine capsules. Suitable carriers for the production of solutions and syrups are, for example, water, polyols, sucrose, invert sugar, glucose and the like. Suitable carriers for suppositories are, for example, natural or hardened oils, waxes, fats, semi-liquid or liquid polyols and the like.

The pharmaceutical preparations can also contain preservatives, solubilizers, stabilizers, wetting agents, emulsifiers, sweeteners, colorants, flavorants, salts for varying the osmotic pressure, buffers, masking agents or antioxidants. They can also contain therapeutically valuable substances other than the compounds of formula I and their aforementioned pharmaceutically acceptable salts.

Medicaments which contain a compound of formula I or a pharmaceutically acceptable salt of a basic compound of formula I with an acid in association with a compatible pharmaceutical carrier material are also an object of the present invention, as is a process for the production of such medicaments which comprises bringing one or more of these compounds or salts and, if desired, one or more other therapeutically valuable substances into a galenical administration form together with a compatible pharmaceutical carrier.

As mentioned earlier, the compounds of formula I and their aforementioned pharmaceutically acceptable salts can be used in accordance with the invention as therapeutically active substances, especially as antiinflammatory agents or for the prevention of graft rejection following transplant surgery. The dosage can vary within wide limits and will, of course, be fitted to the individual requirements in each particular case. In general, in the case of administration to adults a convenient daily dosage should be about 0.1 mg/kg to about 100 mg/kg, preferably about 0.5 mg/kg to about 5 mg/kg. The daily dosage may be administered as a single dose or in divided doses and, in addition, the upper dosage limit referred to earlier may be exceeded when this is found to be indicated.

b) 9 g (237 mmol) of lithium aluminium hydride were stirred in 300 ml of dry tetrahydrofuran and treated dropwise with a solution of 34 g (143 mmol) of ethyl 4-methylamino-2-methylthio-pyrimidine-5-carboxylate in 300 ml of dry tetrahydrofuran and left to stand for 15 minutes. The mixture was cooled in ice and cautiously treated dropwise with 18 ml of water. 36 ml of 2M sodium hydroxide solution were added dropwise, followed by 48 ml of water. The resulting suspension was stirred for 17 hours at room temperature and then filtered. The filter residue was washed twice with 100 ml of ethyl acetate each time and the combined filtrate and washings were evaporated under reduced pressure. The residue was suspended in 200 ml of dichloromethane/hexane (2:1) and the solid was off and dried to give 23.5 g (86%) of 4-methylamino-2-methylthiopyrimidine-5-methanol as a yellow solid.

c) 20 g (108 mmol) of 4-methylamino-2-methylthiopyrimidine-5-methanol were stirred in 1 l of dichloromethane and treated with 87 g (1 mol) of manganese dioxide. The resulting suspension was stirred for 24 hours and then filtered through a filter aid. The filter residue was washed with 100 ml of dichloromethane and the combined filtrate and washings were evaporated under reduced pressure to give 15.8 g (80%) of 4-methylamino-2-methylthiopyrimidine-5-carboxaldehyde as a white solid.

d) A mixture of 6 g (32.8 mmol) of 4-methylamino-2-methylthiopyrimidine-5-carboxaldehyde, 5.5 g (33.9 mmol) of 2,6-dichloroaniline and 1 g (5.3 mmol) of 4-toluenesulphonic acid in 70 ml of toluene was heated under reflux with azeotropic removal of water for 17 hours. The mixture was concentrated to a volume of about 10 ml under reduced pressure and then treated with 120 ml of ethanol. The suspension obtained was heated to 75°C and treated over a period of 15 minutes with 6.2 g (160 mmol) of sodium borohydride pellets. The mixture was stirred for a further 15 minutes and cooled to room temperature. The solvent was evaporated under reduced pressure and the residue was stirred in a mixture of 200 ml of 2M sodium hydroxide solution and 200 ml of ethyl acetate for 1 hour. The phases were separated and the organic phase was dried over magnesium sulphate and filtered. Evaporation of the filtrate under reduced pressure and flash chromatography of the residue using diethyl ether/hexane (3:7) for the elution gave 5.2 g (48%) of 5-(2,6-dichlorophenyl)aminomethyl-4-methylamino-2-methylthio-pyrimidine as a white solid.

e) A stirred solution, cooled in ice, of 12 ml of phosgene (20% solution in toluene; 23 mmol) in 100 ml of tetrahydrofuran was treated dropwise with a solution of 5 g

(15.2 mmol) of 5-(2,6-dichlorophenyl)aminomethyl-4-methylamino-2-methylthio-pyrimidine and 4 ml (29 mmol) of triethylamine in 80 ml of tetrahydrofuran. After stirring for 1 hour the mixture was treated with 100 ml of saturated aqueous ammonium chloride solution and the phases were separated. The aqueous phase was extracted with 100 ml of tetrahydrofuran and the combined organic solutions were dried over magnesium sulphate and filtered. The filtrate was concentrated under reduced pressure to give 4.8 g (89%) of 3-(2,6-dichlorophenyl)-7-methylthio-3,4-dihydro-1-methylpyrimido[4,5-d]pyrimidin-2(1H)-one as a white solid.

f) A solution of 5 g (14.1 mmol) of 3-(2,6-dichlorophenyl)-7-methylthio-3,4-dihydro-1-methylpyrimido[4,5-d]pyrimidin-2(1H)-one in 200 ml of dichloromethane was cooled in ice and treated with 10 g (28.9 mmol) of 3-chloroperbenzoic acid. The mixture was stirred at room temperature for 17 hours, then treated with 2 ml of dimethyl sulphoxide and left to stand for 10 minutes. 100 ml of saturated aqueous sodium bicarbonate solution were then added and the phases were separated. The organic phase was dried over magnesium sulphate and filtered. Concentration of the filtrate under reduced pressure gave 5 g (92%) of 3-(2,6-dichlorophenyl)-7-methanesulphonyl-3,4-dihydro-1-methylpyrimido[4,5-d]pyrimidin-2(1H)-one as a white solid.

The 4-[2-(diethylamino)ethoxy]-aniline used as the starting material was prepared as follows:

i) A solution of 27.8 g (0.2 mol) of 4-nitrophenol in 500 ml of ethanol was treated with 15 g (0.22 mol) of sodium ethoxide. After stirring at room temperature for 30 minutes the solvent was removed under reduced pressure. The residual yellow solid was stirred in a mixture of 160 ml of xylene and 30 ml of water and then treated with 41.4 g (0.3 mol) of potassium carbonate and 34.4 g (0.2 mol) of 2-diethylaminoethyl chloride hydrochloride. The mixture was heated under reflux for 17 hours and filtered while hot. The filter residue was washed with hot xylene and the combined filtrate and washings were evaporated under reduced pressure. Distillation of the residue under a high vacuum gave 31.4 g (66%) of 4-[2-(diethylamino)ethoxy]-nitrobenzene as a liquid.

ii) A solution of 5 g (21 mmol) of 4-[2-(diethylamino)ethoxy]-nitrobenzene in 50 ml of ethanol was hydrogenated over 100 mg of 10% palladium-on-carbon at room temperature and under atmospheric pressure. After 4 hours the suspension was filtered through a filter aid and the filtrate was evaporated under reduced pressure to give 4 g (92%) of 4-[2-(diethylamino)ethoxy]-aniline as an oil.

Example 2

A mixture of 100 mg (0.31 mmol) of 3-(2-chlorophenyl)-7-methanesulphonyl 3,4-dihydro-1-methylpyrimido[4,5-d]pyrimidin-2(1H)-one and 300 mg (1.4 mmol) of 4-[2-(diethylamino)ethoxy]aniline was heated at 180°C for 30 minutes and then cooled. The residue was chromatographed on silica gel using dichloromethane/methanol/acetic acid/water (240:24:3:2) for the elution. Product-containing fractions were combined and evaporated. The residue was evaporated with toluene and then dissolved in 40 ml of dichloromethane. The solution was washed with 40 ml of saturated sodium bicarbonate solution, dried over magnesium sulphate, filtered and evaporated to give 20 mg (15%) of 3-(2-chlorophenyl)-7-[4-[2-(diethylamino)ethoxy]anilino]-3,4-dihydro-1-methyl-pyrimido[4,5-d]pyrimidin-2(1H)-one as a white solid of melting point 150°-151°C.

The 3-(2-chlorophenyl)-7-methanesulphonyl-3,4-dihydro-1-methyl- pyrimidin-2(1H)-one used as the starting material was prepared in an analogous manner to that describred in Example 1 a)-f) using 2-chloroaniline in place of 2,6-dichloroaniline.

Example 3

A mixture of 100 mg (0.31 mmol) of 3-phenyl-7-methanesulphonyl-3,4-dihydro-1-methylpyrimido[4,5-d]pyrimidin-2(1H)-one and 300 mg (1.4 mmol) of 4-[2-(diethyl-amino)ethoxy]aniline was heated at 170-180°C for 10 minutes and then cooled. The residue was chromatographed on silica gel using dichloromethane/methanol/acetic acid/water (240:24:3:2) for the elution. Product-containing fractions were combined and evaporated. The residue was evaporated with toluene and then dissolved in 40 ml of dichloromethane. The solution was washed with 40 ml of saturated sodium bicarbonate solution, dried over magnesium sulphate, filtered and evaporated. The residual solid was purified by crystallization from cyclohexane/ethyl acetate to give 14 mg (10%) of 3-phenyl-7-[4-[2-(diethylamino)ethoxy]anilino]-3,4-dihydro-1-methylpyrimido[4,5-d]pyrimidin-2(1H)-one as a white solid of melting point 141-144°C.

The 3-phenyl-7-methanesulphonyl-3,4-dihydro-1-methylpyrimido[4,5-d]-pyrimidin-2(1H)-one used as the starting material was prepared as follows:

a) 350 mg (1.6 mmol) of sodium triacetoxyborohydride and subsequently 0.1 ml (1.7 mmol) of acetic acid were added to a mixture of 200 mg (1.1 mmol) of 4-methylamino-2-methylthiopyrimidine-5-carboxaldehyde and 110 mg (1.2 mmol) of aniline in 5 ml of 1,2-dichloroethane. After 2.5 hours 25 ml of saturated aqueous sodium bicarbonate and 20 ml of dichloromethane were added. The phases were separated and the aqueous phase was washed twice with 25 ml of dichloromethane. The combined organic solutions were dried over magnesium sulphate, filtered and evaporated. The residue was chromatographed on silica gel using diethyl ether/hexane (1:1) for the elution. Product-containing fractions were combined and evaporated to give 218 mg (76%) of 5-phenylaminomethyl-4-methylamino-2-methylthiopyrimidine as a white solid.

b) A mixture of 200 mg (0.77 mmol) of 5-phenylaminomethyl-4-methylamino-2-methylthiopyrimidine and 0.2 ml (1.4 mmol) of triethylamine in 15 ml of dioxan was added dropwise to a solution, cooled in ice, of 150 mg (0.79 mmol) of trichloromethyl chloroformate in 10 ml of dioxan. The mixture was then left to warm to room temperature. After a further 10 minutes the mixture was evaporated. 40 ml of dichloromethane and 40 ml of saturated aqueous sodium bicarbonate solution were added to the residue. The phases were separated and the dichloromethane phase was dried over magnesium sulphate, filtered and evaporated to give 162 mg (74%) of 3-phenyl-7-methylthio-3,4-dihydro-1-methylpyrimido[4,5-d]pyrimidin-2(1H)-one as a white solid.

c) A solution of 160 mg (0.56 mmol) of 3-phenyl-7-methylthio-3,4-dihydro-1-methylpyrimido[4,5-d]pyrimidin-2(1H)-one in 20 ml of dichloromethane was treated with 400 mg (1.16 mmol) of 3-chloroperbenzoic acid (50% w/w in water). After 3 hours 30 ml of saturated aqueous sodium bicarbonate solution and 20 ml of dichloromethane were added and the phases were separated. The organic phase was dried over magnesium sulphate, filtered and then evaporated to give 165 mg (93%) of 3-phenyl-7-methanesulphonyl-3,4-dihydro-1-methylpyrimido[4,5-d]pyrimidin-2(1H)-one as a white solid.

Example 4

A mixture of 100 mg (0.31 mmol) of 3-cyclohexyl-7-methanesulphonyl-3,4-dihydro-1-methylpyrimido[4,5-d]pyrimidin-2-(1H)-one and 400 mg (1.9 mmol) of 4-[2-(diethylamino)ethoxy]aniline was heated at 180°C for 35 minutes and then cooled. The residue was chromatographed on silica gel using dichloromethane/methanol/acetic acid/water (240:24:3:2) for the elution. Product-containing fractions were combined and

evaporated. The residue was evaporated with toluene and then dissolved in 40 ml of dichloromethane. The solution was washed with 40 ml of saturated aqueous sodium bicarbonate solution, dried over magnesium sulphate, filtered and evaporated. The residue was triturated in hexane, filtered off and dried to give 25 mg (18%) 3-cyclohexyl-7-[4-[2-(diethylamino)ethoxy]anilino]-3,4-dihydro-1-methylpyrimido[4,5-d]pyrimidin-2(1H)-one as a white solid of melting point 90-92°C

The 3-cyclohexyl-7-methanesulphonyl-3,4-dihydro-1-methylpyrimido-[4,5-d]pyrimidin-2(1H)-one used as the starting material was prepared as follows:

a) A mixture of 200 mg (1.1 mmol) of 4-methylamino-2-methylthiopyrimidine-5-carboxaldehyde and 200 mg (2.02 mmol) of cyclohexylamine in 10 ml of methanol was left to stand over 500 mg of type 4A molecular sieves for 3 days. The solution was decanted from the sieves and 100 mg (2.7 mmol) of sodium borohydride were added portionwise thereto. After 30 minutes the mixture was evaporated and 60 ml of ethyl acetate and 60 ml of 2M aqueous sodium hydroxide were added to the residue. The phases were separated and the organic phase was dried over magnesium sulphate, filtered and evaporated to give 245 mg (85%) of 5-cyclohexylaminomethyl-4-methylamino-2-methylthiopyrimidine as a colourless oil.

b) A mixture of 210 mg (0.79 mmol) of 5-cyclohexylaminomethyl-4-methyl-amino-2-methylthiopyrimidine and 0.2 ml of triethylamine in 10 ml of tetrahydrofuran was added dropwise to an ice-cooled solution of 0.5 ml (0.96 mmol) of phosgene (20% solution in toluene) in 5 ml of tetrahydrofuran. After 1 hour 15 ml of aqueous ammonium chloride solution and 10 ml of tetrahydrofuran were added to the resulting mixture. The phases were separated. The organic phase was dried over magnesium sulphate, filtered and then evaporated. The residue was chromatographed on silica gel using diethyl ether/hexane (3:2) for the elution. Product-containing fractions were combined and evaporated to give 120 mg (52%) of 3-cyclohexyl-7-methylthio-3,4-dihydro-1-methylpyrimido[4,5-d]pyrimidin-2(1H)-one as a white solid.

c) A solution of 100 mg (0.34 mmol) 3-cyclohexyl-7-methylthio-3,4-dihydro-1-methylpyrimido[4,5-d]pyrimidin-2(1H)-one in 10 ml of dichloromethane was treated with 250 ml (0.74 mmol) of 3-chloroperbenzoic acid (50% w/w water). After 3 hours 30 ml of saturated aqueous sodium bicarbonate solution and 20 ml of dichloromethane were added and the phases were separated. The organic phase was dried over magnesium

sulphate, filtered and then evaporated to give 165 mg (93%) of 3-cyclohexyl-7-methanesulphonyl-3,4-dihydro-1-methylpyrimido[4,5-d]pyrimidin-2(1H)-one as a white solid.

Example 5

A mixture of 250 ml (0.83 mmol) of 3-tert.butyl-7-methanesulphonyl-3,4-dihydro-1-methylpyrimido[4,5-d]pyrimidin-2(1H)-one and 600 mg (2.9 mmol) of 4-(2-(diethylamino)ethoxy)aniline was heated at 180°C for 35 minutes and then cooled. The residue was chromatographed on silica gel using dichloromethane/methanol/ acetic acid/water (240:24:3:2) for the elution. Product-containing fractions were combined and evaporated. The residue was evaporated with toluene and then dissolved in 30 ml of dichloromethane. The solution was washed with 20 ml of saturated aqueous sodium bicarbonate solution, dried over magnesium sulphate, filtered and evaporated. The residue was triturated in hexane, filtered off and dried to give 70 mg (21%) of 3-tert.butyl-7-[4-[2-(diethylamino)-ethoxy]anilino]-3,4-dihydro-1-methylpyrimido[4,5-d]pyrimidin-2(1H)-one as an off-white solid of melting point 130°C.

The 3-tert.butyl-7-methanesulphonyl-3,4-dihydro-1-methylpyrimido[4,5-d]-pyrimidin-2(1H)-one used as the starting material was prepared as follows:

a) A mixture of 200 mg (1.1 mmol) of 4-methylamino-2-methylthiopyrimidine-5-carboxaldehyde and 0.23 ml (2.18 mmol) of tert.butylamine in 10 ml of methanol was left to stand over 500 mg of type 4A molecular sieves for 3 days. The solution was decanted from the sieves and 100 mg (2.7 mmol) of sodium borohydride were added portionwise thereto. After 30 minutes the mixture was evaporated and 20 ml of ethyl acetate and 20 ml of 2M aqueous sodium hydroxide were added to the residue. The phases were separated and the organic phase was dried over magnesium sulphate, filtered and evaporated to give 240 mg (92%) of 5-tert.butylaminomethyl-4-methylamino-2-methylthiopyrimidine as a white solid.

b) A mixture of 240 mg (1 mmol) of 5-tert.butylaminomethyl-4-methylamino-2-methylthiopyrimidine and 0.28 ml of triethylamine in 5 ml of tetrahydorfuran was added dropwise to an ice-cooled solution of 1 ml (1.92 mmol) of phosgene (20% solution in toluene) in 5 ml of tetrahydrofuran. After 1 hour 30 ml of saturated aqueous ammonium chloride and 20 ml of tetrahydrofuran were added to the resulting mixture. The phases

were separated. The organic phase was dried over magnesium sulphate, filtered and then evaporated to give 220 mg (83%) of 3-tert.butyl-7-methylthio-3,4-dihydro-1-methyl-pyrimido[4,5-d]pyrimidin-2(1H)-one as a white solid.

c) A solution of 220 mg (0.83 mmol) of 3-tert.butyl-7-methylthio-3,4-dihydro-1-methylpyrimido[4,5-d]pyrimidin-2(1H)-one in 20 ml of dichloromethane was treated with 570 mg (1.66 mmol) of 3-chloroperbenzoic acid (50% w/w in water). After 18 hours 0.2 ml of saturated aqueous sodium bicarbonate solution was added and the phases were separated. The organic phase was washed with 20 ml of saturated aqueous sodium bicarbonate solution, dried over magnesium sulphate, filtered and then evaporated to give 250 mg (100%) of 3-tert.butyl-7-methanesulphonyl-3,4-dihydro-1-methylpyrimido[4,5-d]pyrimidin-2(1H)-one as a white solid.

Example 6

A mixture of 200 mg (0.65 mmol) of 3-cyclopentyl-7-methanesulphonyl-3,4-dihydro-1-methylpyrimido[4,5-d]pydrimidin-2(1H)-one and 300 mg (1.4 mmol) of 4-[2-(diethylamino)ethoxy]aniline was heated at 180°C for 35 minutes and then cooled. The residue was chromatographed on silica gel using dichloromethane/ methanol/acetic acid/water (240:24:3:2) for the elution. Product-containing fractions were combined and evaporated. The residue was evaporated with toluene and then dissolved in 30 ml of dichloromethane. The solution was washed with 20 ml of saturated aqueous sodium bicarbonate solution, dried over magnesium sulphate, filtered and evaporated. The residue was purified by reverse-phase high performance liquid chromatography (HPLC). The mobile phase was water/0.1% trifluroacetic acid (A) and acetonitrile/0.07% trifluoroacetic acid (B); the gradient was 5%-95% B over 20 minutes; and the product was detected using an ultraviolet detector at a wavelength of 215 nm. Product-containing fractions were lyophilized to give 20 mg (7%) of 3-cyclopentyl-7-[4-[2-(diethylamino)ethoxy]anilino]-3,4-dihydro-1-methylpyrimido[4,5-d]pydrimidin-2(1H)-one trifluoroacetate as a white solid of melting point 89°C.

The 3-cyclopentyl-7-methanesulphonyl-3,4-dihydro-1-methylpyrimido[4,5-d]-pyrimidin-2(1H)-one used as the starting material was prepared in an analogous manner to that described in Example 5 a)-c) using cyclopentylamine in place of tert.butyl- amine.

Example 7

A mixture of 120 mg (0.27 mmol) of 3-(2,6-dichlorophenyl)-7-methanesulphonyl-3,4-dihydro-1-phenylpyrimido[4,5-d]pyrimidin-2(1H)-one and 370 mg (1.8 mmol) of 4-[2-(diethylamino)ethoxy]aniline was heated at 180°C for 40 minutes and then cooled. The residue was chromatographed on silica gel using dichloromethane/methanol/acetic acid/water (240:24:3:2) for the elution. Product-containing fractions were combined and evaporated. The residue was evaporated with toluene and then dissolved in 50 ml of dichloromethane. The solution was washed with 50 ml of saturated aqueous sodium bicarbonate solution, dried over magnesium sulphate, filtered and evaporated. The residual solid was purified by crystallization from cyclohexane/ethyl acetate to give 10 mg (6%) of 3-(2,6-dichlorophenyl)-7-[4-[2-(diethylamino)ethoxy]anilino]-3,4-dihydro-1-phenylpyrimido[4,5-d]pyrimidin-2(1H)-one as an off-white solid of melting point 162-163°C.

The 3-(2,6-dichlorophenyl)-7-methanesulphonyl-3,4-dihydro-1-phenylpyrimido-[4,5-d]pyrimidin-2(1H)-one used as the starting material was prepared as follows:

a) A mixture of 4 g (17.2 mmol) of ethyl 4-chloro-2-methylthiopyrimidine-5-carboxylate and 5 g (54 mmol) of aniline in 40 ml of dioxan was stirred at room temperature for 24 hours. The mixture was then evaporated and 100 ml of ethyl acetate and 50 ml of 2M aqueous hydrochloric acid were added to the residue. The phases were separated and the organic phase was washed with 50 ml of aqueous hydrochloric acid, dried over magnesium sulphate, filtered and evaporated. The resulting solid was purified by crystallization from aqueous ethanol to give 3.5 g (64%) of ethyl 4-phenylamino-2-methylthiopyrimidine-5-carboxylate as a white solid.

b) A solution of 3.5 g (11.1mmol) of ethyl 4-phenylamino-2-methylthiopyrimidine-5-carboxylate in 50 ml of tetrahydrofuran was cooled in ice and then treated dropwise with 12 ml (12 mmol) of 1M lithium aluminium hydride in tetrahydrofuran. The cooling was removed and the mixture was stirred at room temperature for 3 hours. The mixture was then cooled in ice and cautiously treated dropwise with 0.5 ml of water, 0.75 ml of 2M aqueous sodium hydroxide and then 1 ml of water. The resulting suspension was filtered through a filter aid. The filtrate was evaporated to give 2.7 g (98%) of 4-phenylamino-2-methylthiopyrimidine-5-methanol as a yellow oil.

c) 2.7 g (10.9 mmol) of 4-phenylamino-2-methylthiopyrimidine-5-methanol were stirred in 50 ml of dichloromethane and treated with 9.6 g (111 mmol) of manganese dioxide. The suspension was stirred for 18 hours and then filtered through a filter aid. The filtrate was evaporated and the residue was chromatographed on silica gel using diethyl ether/hexane (1:1) for the elution. Product-containing fractions were combined and evaporated to give 1.8 g (67%) of 4-phenylamino-2-methylthiopyrimidine-5-carboxaldehyde as a white solid.

d) A mixture of 700 mg (2.9 mmol) of 4-phenylamino-2-methylthiopyrimidine-5-carboxaldehyde, 490 mg (3.0 mmol) of 2,6-dichloroaniline and 100 mg (0.5 mmol) of 4-toluenesulphonic acid in 50 ml of toluene was heated at reflux with the azeotropic removal of water for 18 hours. The mixture was cooled and evaporated. 50 ml of methanol and 400 mg (11.7 mmol) of sodium borohydride were added and the mixture was heated at reflux for 20 minutes, cooled and then evaporated. The residue was stirred in a mixture of 50 ml of 2M aqueous sodium hydroxide and 50 ml of ethyl acetate for 30 minutes and then the phases were separated. The organic phase was dried over magnesium sulphate, filtered and evaporated. Flash chromatography of the residue on silica gel using diethyl ether/ hexane (2:3) for the elution gave 410 mg (36%) of 5-(2,6-dichlorophenyl)aminomethyl-4-phenylamino-2-methylthiopyrimidine as a white solid.

e) A stirred solution, cooled in ice, of 0.25 ml (0.48 ml) of phosgene (20% in toluene) in 5 ml of tetrahydrofuran was treated dropwise with a solution of 100 mg (0.26 mmol) of 5-(2,6-dichlorophenyl)aminomethyl-4-phenylamino-2-methylthiopyrimidine and 0.1 ml (0.7 mmol) of triethylamine in 10 ml of tetrahydrofuran. The mixture was stirred at room temperature for 3 days. 20 ml of tetrahydrofuran and 20 ml of saturated aqueous ammonium chloride solution were added, the phases were separated and the organic phase was dried over magnesium sulphate, filtered and evaporated to give 110 mg (100%) of 3-(2,6-dichlorophenyl)-7-methylthio-3,4-dihydro-1-phenylpyrimido[4,5-d]pyrimidin-2(1H)-one as a white solid.

f) A solution of 110 mg (0.26 mmol) of 3-(2,6-dichlorophenyl)-7-methylthio-3,4-dihydro-1-phenylpyrimido[4,5-d]pyrimidin-2(1H)-one in 5 ml of dichloromethane was treated with 190 mg (0.55 mmol) of 3-chloroperbenzoic acid (50% w/w in water). After 18 hours 40 ml of saturated aqueous sodium bicarbonate solution and 40 ml of dichloromethane were added and the phases were separated. The organic phase was dried over

magnesium sulphate, filtered and evaporated to give 120 mg (100%) of 3-(2,6-dichlorophenyl)-7-methanesulphonyl-3,4-dihydro-1-phenylpyrimido[4,5-d]pyrimidin-2(1H)-one as a pale yellow oil.

Example 8

A mixture of 100 mg (0.25 mmol) of 3-(2,6-dichlorophenyl)-1-ethyl-7-methanesulphonyl-3,4-dihydropyrimido[4,5-d]pyrimidin-2(1H)-one and 120 mg (0.5 mmol) of 4-[2-(diethylamino)ethoxy]aniline was heated at 180°C for 35 minutes and then cooled. The residue was chromatographed on silica gel using dichloromethane/methanol/acetic acid/water (240:24:3:2) for the elution. Product-containing fractions were combined and evaporated. The residue was evaporated with toluene and then dissolved in 50 ml of dichloromethane. The solution was washed with 50 ml of saturated aqueous sodium bicarbonate solution, dried over magnesium sulphate, filtered and evaporated to give 30 mg (22%) of 3-(2,6-dichlorophenyl)-1-ethyl-7-[4-[2-(diethylamino)ethoxy]anilino]-3,4-dihydropyrimido[4,5-d]pyrimidin-2(1H)-one as an orange coloured solid of melting point 85°C.

The 3-(2,6-dichlorophenyl)-1-ethyl-7-methanesulphonyl-3,4-dihydro-pyrimido-[4,5-d]pyrimidin-2(1H)-one used as the starting material was prepared as follows:

a) A mixture of 49 g (246 mmol) of 4-amino-5-carbethoxypyrimidine-2-thiol and 42 g (304 mmol) of potassium carbonate in 400 ml of acetone was treated with 50 g (352 mmol) of iodomethane. After stirring for 3 hours 500 ml of water were added. The phases were separated and the aqueous phase was extracted twice with 300 ml of dichloromethane each time. The combined organic phases were washed with 100 ml of brine , dried over magnesium sulphate, filtered and evaporated to give 45.2 g (86%) of ethyl 4-amino-2-methylthiopyrimidine-5-carboxylate as a pale yellow solid.

b) 13 g (338 mmol) of lithium aluminium hydride were stirred in 300 ml of tetrahydrofuran and treated dropwise with a solution of 45 g (211 mmol) of ethyl 4-amino-2-methylthiopyrimidine-5-carboxylate in 300 ml of tetrahydrofuran. 15 minutes after completion of the addition the mixture was cooled in ice and cautiously treated dropwise with 25 ml of water. After stirring for 2 hours at room temperature the mixture was filtered through a filter aid and the filtrate was evaporated. The residue was triturated in

500 ml of dichloromethane/hexane (1:1), collected by filtration and dried to give 28 g (78%) of 4-amino-2-methylthiopyrimidine-5-methanol as a white solid.

c) 28 g (164 mmol) of 4-amino-2-methylthiopyrimidine-5-methanol were stirred in 500 ml of dichloromethane and treated with 150 g (1.7 mol) of manganese dioxide. The suspension was stirred for 24 hours and then filtered through a filter aid. The filtrate was evaporated to give 20.2 g (73%) of 4-amino-2-methylthiopyrimidine 5-carboxaldehyde as a pale yellow solid.

d) A mixture of 10 g (59.2 mmol) of 4-amino-2-methylthiopyrimidine-5-carboxaldehyde, 9.7 g (59.9 mmol) of 2,6-dichloroaniline and 1 g (5.3 mmol) of 4-toluenesulphonic acid in 200 ml of xylene was heated at reflux with the azeotropic removal of water for 24 hours. The mixture was cooled and evaporated. 50 ml of acetic acid and 20 ml of toluene were added to the residue. The mixture was cooled in ice and treated portionwise over 30 minutes with 5 g (147 mmol) of sodium borohydride. After 1 hour the mixture was evaporated and the residue was stirred in a mixture of 100 ml of ethyl acetate and 100 ml of 2M aqueous sodium hydroxide for 1 hour. The phases were separated and the organic phase was dried over magnesium sulphate, filtered and evaporated. Crystallization of the residue from aqueous ethanol gave 2.4 g (13%) of 5-(2,6-dichlorophenyl)aminomethyl-4-amino-2-methylthiopyrimidine as a white solid. The mother liquors were evaporated and flash chromatography of the residue on silica gel using diethyl ether/ hexane (1:1) for the elution gave a further 2.1 g (11%) of 5-(2,6-dichlorophenyl)aminomethyl-4-amino-2-methylthiopyrimidine as a white solid.

e) A stirred solution, cooled in ice, of 5.8 ml (11.2 mmol) of phosgene (20% in toluene) in 80 ml of tetrahydrofuran was treated dropwise with a solution of 1.76 g (5.6 mmol) of 5-(2,6-dichlorophenyl)aminomethyl-4-amino-2-methylthiopyrimidine and 1.6 ml (11.2 mmol) of triethylamine in 80 ml of tetrahydrofuran. The mixture was stirred for 1 hour. 50 ml of tetrahydrofuran and 50 ml of saturated aqueous ammonium chloride solution were added. The phases were separated and the organic phase was washed with saturated aqueous ammonium chloride solution, dried over magnesium sulphate, filtered and evaporated to give 1.7 g (89%) of 3-(2,6-dichlorophenyl)-7-methylthio-3,4-dihydropyrimido[4,5-d]pyrimidin-2(1H)-one as a white solid.

f) A solution of 220 mg (0.64 mmol) of 3-(2,6-dichlorophenyl)-7-methylthio-3,4-dihydropyrimido[4,5-d]pyrimidine-2(1H)-one in 10 ml of dichloromethane was treated

with 440 mg (1.28 mmol) of 3-chloroperbenzoic acid (50% w/w in water) and stirred for 18 hours. 0.2 ml of dimethyl sulphoxide was added. After a further 15 minutes 15 ml of saturated aqueous sodium bicarbonate solution were added. The phases were separated and then the organic phase was washed with 30 ml of saturated aqueous sodium bicarbonate solution, dried over magnesium sulphate and evaporated to give 250 mg (100%) of 3-(2,6-dichlorophenyl)-7-methanesulphonyl-3,4-dihydropyrimido[4,5-d]pyrimidin-2(1H)-one as a white solid.

g) A solution, cooled in ice, of 100 mg (0.27 ml) of 3-(2,6-dichlorophenyl)-7-methanesulphonyl-3,4-dihydropyrimido[4,5-d]pyrimidin-2(1H)-one in 6 ml of dimethylformamide was treated with 11 mg (0.27 mmol) of sodium hydride (60% w/w). After 30 minutes the mixture was treated with 0.03 ml (0.3 mmol) of iodoethane and then heated to 90°C for 2 hours. The mixture was evaporated and the residue was treated with 30 ml of dichloromethane and 30 ml of water. The phases were separated and the organic phase was washed with 30 ml of water, dried over magnesium sulphate, filtered and evaporated to give 100 mg (92%) of 3-(2,6-dichlorophenyl)-1-ethyl-7-methanesulphonyl-3,4-dihydropyrimido[4,5-d]pyrimidin-2(1H)-one as a yellow solid.

Example 9

A mixture of 100 mg (0.22 mmol) of 1-benzyl-3-(2,6-dichlorophenyl)-7-methanesulphonyl-3,4-dihydropyrimido[4,5-d]pyrimidin-2(1H)-one and 120 mg (0.5 mmol) of 4-[2-(diethylamino)ethoxy]aniline was heated at 180°C for 35 minutes and then cooled. The residue was chromatographed on silica gel using dichloromethane/methanol/acetic acid/water (240:24:3:2) for the elution. Product-containing fractions were combined and evaporated. The residue was evaporated with toluene and then dissolved in 50 ml of dichloromethane. The solution was washed with 50 ml of saturated aqueous sodium bicarbonate solution, dried over magnesium sulphate, filtered and evaporated to give 30 mg (23%) of 1-benzyl-3-(2,6-dichlorophenyl)-7-[4-[2-(diethylamino)ethoxy]-anilino]-3,4-dihydropyrimido[4,5-d]pyrimidin-2(1H)-one as a white solid of melting point 106°C.

The 1-benzyl-3-(2,6-dichlorophenyl)-7-methanesulphonyl-3,4-dihydro-pyrimido[4,5-d]pyrimidin-2(1H)-one used as the starting material was prepared as follows:

A solution, cooled in ice, of 100 mg (0.27 mmol) of 3-(2,6-dichlorophenyl)-7-methanesulphonyl-3,4-dihydropyrimido[4,5-d]pyrimidin-2(1H)-one in 6 ml of dimethylformamide was treated with 11 mg (0.27 ml) of sodium hydride (60% w/w). After 30 minutes the mixture was treated with 0.04 ml (0.3 mmol) of benzyl bromide and then heated to 90°C for 2 hours. The mixture was evaporated and 30 ml of dichloromethane and 30 ml of water were added to the residue. The phases were separated and the organic phase was washed with 30 ml of water, dried over magnesium sulphate, filtered and evaporated to give 100 mg (80%) of 1-benzyl-3-(2,6-dichlorophenyl)-7-methanesulphonyl-3,4-dihydropyrimido[4,5-d]pyrimidin-2(1H)-one as a yellow solid.

Example 10

A mixture of 60 mg (0.13 mmol) of 3-(2,6-dichlorophenyl)-7-methanesulphonyl-3,4-dihydro-1-[(3-pyridyl)methyl]pyrimido[4,5-d]pyrimidin-2(1H)-one and 150 mg (0.72 mmol) of 4-[2-(diethylamino)ethoxy]aniline was heated at 180°C for 35 minutes and then cooled. The residue was chromatographed on silica gel using dichloromethane/methanol/acetic acid/water (240:24:3:2) for the elution. Product-containing fractions were combined and evaporated. The residue was evaporated with toluene and then dissolved in 50 ml of dichloromethane, washed with 50 ml of saturated aqueous sodium bicarbonate solution, dried over magnesium sulphate, filtered and evaporated. The residue was purified by reverse-phase HPLC. The mobile phase was water/0.1% trifluoroacetic acid (A) and acetonitrile/0.07% trifluoroacetic acid (B). The gradient was 5%-95% B over 20 minutes, with the product being detected using an ultraviolet detector at a wavelength of 215 nm. Product-containing fractions were lyophilized to give 16 mg (17%) of 3-(2,6-dichlorophenyl)-7-[4-[2-(diethylamino)ethoxy]anilino]-3,4-dihydro-1-[(3-pyridyl)- methyl]pyrimido[4,5-d]pyrimidin-2(1H)-one trifluroacetate as a white solid of melting point 64°C.

The 3-(2,6-dichlorophenyl)-7-methanesulphonyl-3,4-dihydro-1-[(3-pyridyl)-methyl]pyrimido[4,5-d]pyrimidin-2(1H)-one used as the starting material was prepared as follows:

An ice-cooled solution of 100 mg (0.27 mmol) of 3-(2,6-dichlorophenyl)-7-methanesulphonyl-3,4-dihydropyrimido[4,5-d]pyrimidin-2(1H)-one in 6 ml of dimethylformamide was treated with 22 mg (0.54 mmol) of sodium hydride (60% w/w). After 30 minutes the mixture was treated with 50 mg (0.3 mmol) of picolyl chloride

hydrochoride and then heated to 90°C for 2 hours and to 100°C for a further hour. The mixture was evaporated and the residue was treated with 30 ml of dichloromethane and 30 ml of water. The phases were separated and the organic phase was washed with 30 ml of water, dried over magnesium sulphate, filtered and evaporated to give 60 mg (48%) of 3-(2,6-dichlorophenyl)-7-methanesulphonyl-3,4-dihydro-1-[(3-pyridyl)methyl]-pyrimido[4,5-d]pyrimidin-2(1H)-one as a yellow solid.

Example 11

A mixture of 110 mg (0.29 mmol) of 3-(2,6-dichlorophenyl)-7-methane-sulphonyl-3,4-dihydro-1-methylpyrimido[4,5-d]pyrimidin-2(1H)-one and 0.31 ml (2.9 mmol) of benzylamine was heated at 180°C for 10 minutes and then cooled. 30 ml of ethyl acetate and 30 ml of 2M aqueous hydrochloric acid were added to the residue. The phases were separated and the organic phase was washed in sequence with 20 ml of 5% aqueous sodium bicarbonate solution and 20 ml of brine, dried over magnesium sulphate, filtered and evaporated to give 93 mg (79%) of 7-benzylamino-3-(2,6-dichlorophenyl)-3,4-dihydro-1-methylpyrimido[4,5-d]pyrimidin-2(1H)-one as a white solid of melting point 195-198°C.

Example 12

A mixture of 100 mg (0.26 mmol) of 3-(2,6-dichlorophenyl)-7-methane-sulphonyl-3,4-dihydro-1-methylpyrimido[4,5-d]pyrimidin-2(1H)-one and 0.25 ml (2.6 mmol) of 4-fluoroaniline was heated at 180°C for 30 minutes and then cooled. 30 ml of ethyl acetate and 30 ml of 2M hydrochloric acid were added to the residue. The phases were separated and the organic phase was washed with 20 ml of brine, dried over magnesium sulphate, filtered and evaporated. The residue was chromatographed on silica gel using ethyl acetate/hexane (2:3) for the elution. Product-containing fractions were combined and evaporated to give 40 mg (37%) of 3-(2,6-dichlorophenyl)-7-(4-fluoroanilino)-3,4-dihydro-1-methylpyrimido[4,5-d]- pyrimidin-2(1H)-one as a light grey solid of melting point 208-211°C.

Example 13

A mixture of 100 mg (0.26 mmol) of 3-(2,6-dichlorophenyl)-7-methane-sulphonyl-3,4-dihydro-1-methylpyrimido[4,5-d]pyrimido-2(1H)-one and 0.24 ml

(2.6 mmol) of aniline was heated at 180°C for 30 minutes and then cooled. 30 ml of ethyl acetate and 30 ml of 2M aqueous hydrochloric acid were added to the residue. The phases were separated and the organic phase was washed with 20 ml of brine, dried over magnesium sulphate, filtered and evaporated. The residue was chromatographed on silica gel using ethyl acetate/hexane (1:1) for the elution. Product-containing fractions were combined and evaporated to give 42 mg (40%) of 7-anilino-3-(2,6-dichlorophenyl)-3,4-dihydro-1-methylpyrimido[4,5-d]pyrimidin-2(1H)-one as a pale purple solid of melting point 222-224°C.

Example 14

A mixture of 100 mg (0.26 mmol) of 3-(2,6-dichlorophenyl)-7-methanesulphonyl-3,4-dihydro-1-methylpyrimido[4,5-d]pyrimidin-2(1H)-one and 0.32 ml (2.6 mmol) of 4-methoxyaniline was heated at 60°C for 4 hours and then cooled. 10 ml of 2M aqueous hydrochloric acid were added to the residue. The precipitated yellow solid was filtered off, washed in sequence with 2M aqueous hydrochloric acid, water and diethyl ether and then dried to give 45 mg (40%) of 3-(2,6-dichlorophenyl)-3,4-dihydro-7-(4-methoxyanilino)-1-methylpyrimido[4,5-d]pyrimidin-2(1H)-one as a yellow solid of melting point 175°C (decomposition).

Example 15

A mixture of 200 mg (0.52 mmol) of 3-(2,6-dichlorophenyl)-7-methanesulphonyl-3,4-dihydro-1-methylpyrimido[4,5-d]pyrimidin-2(1H)-one and 140 mg (0.8 mmol) of 4-[2-(dimethylamino)ethoxy]aniline was heated at 160°C for 2 hours and then cooled. The residue was chromatographed on silica gel using firstly dichloromethane/methanol/acetic acid/water (240:24:3:2) and then dichloromethane/methanol/acetic acid/water (90:18:3:2) for the elution. Product-containing fractions were combined and evaporated. The residue was evaporated with toluene and then dissolved in 40 ml of dichloromethane, washed with 40 ml of saturated aqueous sodium bicarbonate solution, dried over magnesium sulphate, filtered and evaporated to give 35 mg (23%) of 3-(2,6-dichlorophenyl)-7-[4-[2-(dimethylamino)ethoxy]anilino]-3,4-dihydro-1-methylpyrimido[4,5-d]pyrimidin-2(1H)-one as a white solid of melting point 173-174°C.

The 4-[2-(dimethylamino)ethoxy]aniline used as the starting material was prepared as follows:

a) A suspension of 5 g (36 mmol) of 4-nitrophenol in 250 ml of xylene was treated with a solution of 1.63 g (41 mmol) of sodium hydroxide in 20 ml of water and the mixture was stirred at room temperature for 30 minutes. The mixture was then treated with 7.5 g (54 mmol) of potassium carbonate and 5.11 g (36 mmol) of dimethylaminoethyl chloride hydrochloride. The mixture was heated at reflux for 2 hours and then for a further 24 hours with azeotropic removal of water. The mixture was filtered while hot and the solid was washed with hot xylene. The combined filtrate and washings were evaporated and the residue was distilled under a high vacuum to give 1.28 g (20%) of 4-[2-dimethyl-amino)ethoxy]nitrobenzene as an orange coloured liquid.

b) A solution of 880 mg (3.7 mmol) of 4-[2-dimethylamino)ethoxy]nitrobenzene in 10 ml of ethanol was hydrogenated at atmospheric pressure over 88 mg of 10% palladium on charcoal for 3 hours. The suspension was filtered through a pad of filter aid and the filtrate was evaporated to give 680 mg (100%) of 4-[2-(dimethylamino)ethoxy]aniline as an orange coloured liquid.

Example 16

(a) A mixture of 200 mg (0.52 mmol) of 3-(2,6-dichlorophenyl)-3,4-dihydro-7-methanesulphonyl-1-methylpyrimido[4,5-d]pyrimidin-2(1H)-one and 800 mg (4.47 mmol) of ethyl 4-aminophenylacetate was heated at 185°C for 45 minutes. The residue was partitioned between 10 ml of ethyl acetate and 10 ml of 2M hydrochloric acid and the insoluble cream coloured solid was collected by filtration and washed with 20 ml of water and 20 ml of ethyl acetate and then dried under a high vacuum. 95 mg (38%) of ethyl 2-[4-[[3-(2,6-dichlorophenyl)-1,2,3,4-tetrahydro-1-methyl-2-oxopyrimido[4,5-d]pyrimidin-7-yl]amino]phenyl]acetate of melting point 211-212°C were isolated.

b) A 1.0M solution of lithium aluminium hydride in anhydrous terahydrofuran (91 µl; 91 µmol) was added dropwise to a stirred solution of 40 mg (82 µmol) of ethyl 2-[4-[[3-(2,6-dichlorophenyl)-1,2,3,4-tetrahydro-1-methyl-2-oxopyrimido[4,5-d]-pyrimidin-7-yl]amino]phenyl]acetate in 4 ml of anhydrous tetrahydrofuran at 0°C and the mixture was stirred for a further 90 minutes. The reaction was quenched with10 ml of 2M sodium hydroxide and the mixture was extracted twice with 10 ml of ethyl acetate each time. The combined organic extracts were dried over magnesium sulphate, filtered and

evaporated. The residue was purified by flash column chromatography on silica gel using ethyl acetate/hexane (2:1) for the elution. Product-containing fractions were evaporated to give 25mg (68%) of 3-(2,6-dichlorophenyl)-3,4-dihydro-7-[4-(2-hydroxyethyl)anilino]-1-methylpyrimido[4,5-d]pyrimidin-2(1H)-one as a white solid of melting point 148-151°C.

The ethyl 4-aminophenylacetate used as the starting material was prepared as follows:

A solution of 1 g(4.78 mmol) of ethyl-4-nitrophenylacetate in 10 ml of dry methanol was treated with 100 mg of 10% palladium-on-carbon and then hydrogenated at room temperature and at atmospheric pressure for 4 hours. The catalyst was removed by filtration and the filtrate was evaporated to give 830 mg (97%) of ethyl 4-aminophenyl-acetate as a mobile yellow oil.

Example 17

A mixture of 100 mg (0.26 mmol) of 3-(2,6-dichlorophenyl)-3,4-dihydro-7-methanesulphonyl-1-methylpyrimido[4,5-d]pyrimidin-2(1H)-one and 400 µl (3.4 mmol) of phenethylamine was heated at 180°C for 4 hours and then cooled to room temperature. The mixture was dissolved in 10 ml of ethyl acetate and washed in sequence with 10 ml of 2M hydrochloric acid and 10 ml of saturated aqueous sodium bicarbonate solution. The ethyl acetate phase was separated, dried over magnesium sulphate, filtered and evaporated. The crude product was purified by flash column chromatography on silica gel using 5% methanol/dichloromethane for the elution. Product-containing fractions were combined and evaporated to give 35 mg of 3-(2,6-dichlorophenyl)-3,4-dihydro-1-methyl-7-(2-phenylethylamino)pyrimido[4,5-d]pyrimidin-2(1H)-one as a pale yellow solid of melting point 148-151°C.

Example 18

A mixture of 2.2 g (5.7 mmol) of 3-(2,6-dichlorophenyl)-3,4-dihydro-7-methanesulphonyl-1-methylpyrimido[4,5-d]pyrimidin-2(1H)-one and 4.8 g (28.5 mmol) of 2,4-dimethoxybenzylamine was heated at 55°C for 2 hours and then left to cool. The mixture was dissolved in 100 ml of dichloromethane and washed in sequence with 30 ml of 2M hydrochloric acid, 30 ml of saturated aqueous sodium bicarbonate solution and 30 ml of

brine. The organic phase was separated, dried over magnesium sulphate, filtered and evaporated. The residue was triturated with ethyl acetate/hexane (1:1) and 3-(2,6-dichlorophenyl)-3,4-dihydro-7-(2,4-dimethoxybenzylamino)-1-methylpyrimido[4,5-d]-pyrimidin-2(1H)-one was collected by filtration as a white solid which was dried at 40°C under a high vacuum. The yield was 2.35 g (87%) after drying and the melting point was 152-154°C.

Example 19

A solution of 200 mg (0.42 mmol) of 3-(2,6-dichlorophenyl)-3,4-dihydro-7-(2,4-dimethoxybenzylamino)-1-methylpyrimido[4,5-d]pyrimidin-2(1H)-one in 2 ml of dichloromethane was treated with 2 ml of trifluoroacetic acid and the mixture was stirred at room temperature under a nitrogen atmosphere for 5 hours. The solvent was evaporated, the residue was triturated with saturated aqueous sodium bicarbonate solution and the product was collected by filtration and sucked dry. The dried product was purified further by suspension in dichloromethane and filtration through a polytetrafluoroethylene membrane. The filtrate was evaporated and the residue was dried to give 115 mg (84%) of 7-amino-3-(2,6-dichlorophenyl)-3,4-dihydro-1-methylpyrimido[4,5-d]pyrimidin-2(1H)-one as a white solid of melting point 176-184°C.

Example 20

A solution of 100 mg (0.22 mmol) of 3-(2,6-dichlorophenyl)-7-methanesulphonyl-1-phenyl-3,4-dihydro-1H-pyrimido[4,5-d]pyrimidin-2-one and 300 µl (2.4 mmol) of cyclohexylamine in 2 ml of dichloromethane was stirred at room temperature overnight. The mixture was diluted with 10 ml of dichloromethane, washed with 10 ml of 2M hydrochloric acid and with 10 ml of saturated aqueous sodium bicarbonate solution, dried over magnesium sulphate, filtered and evaporated. 99 mg (96%) of 3-(2,6-dichlorophenyl)-7-cyclohexylamino-3,4-dihydro-1-phenylpyrimido[4,5-d]pyrimidin-2(1H)-one were isolated as a white foam of melting point 258-259°C.

Example 21

A solution of 100 mg (0.22 mmol) of 3-(2,6-dichlorophenyl)-7-methanesulphonyl-1-phenyl-3,4-dihydro-1H-pyrimido[4,5-d]pyrimidin-2-one and 2 ml of methylamine in

tetrahydrofuran was stirred at room temperature for 48 hours. The mixture was diluted with 10 ml of ethyl acetate, washed with 10 ml of 2M hydrochloric acid and with 10 ml of saturated aqueous sodium bicarbonate solution, dried over magnesium sulphate, filtered and evaporated. 30 mg (34%) of 3-(2,6-dichlorophenyl)-3,4-dihydro-7-methylamino-1-phenylpyrimido[4,5-d]pyrimidin-2(1H)-one were isolated as a white solid of melting point 211-213°C.

Example 22

A solution of 100 mg (0.22 mmol) of 3-(2,6-dichlorophenyl)-7-methanesulphonyl-1-phenyl-3,4-dihydro-1H-pyrimido[4,5-d]pyrimidin-2-one and 200 mg (2.12 mmol) of 4-aminopyridine in 2 ml of dichloromethane was stirred at room temperature overnight. The mixture was evaporated and the residue was purified by flash column chromatography on silica gel using 10% methanol/dichloromethane for the elution. Product containing fractions were combined and evaporated to give 16 mg (15%) of 3-(2,6-dichlorophenyl)-3,4-dihydro-1-phenyl-7-[(4-pyridyl)amino]pyrimido[4,5-d]pyrimidin-2(1H)-one as an off-white solid which decomposed at 289°C.

Example 23

A solution of 100 mg (0.22 mmol) of 3-(2,6-dichlorophenyl)-7-methanesulphonyl-1-phenyl-3,4-dihydro-1H-pyrimido[4,5-d]pyrimidin-2-one and 285 µl (2.2 mmol) of cyclohexylmethylamine in 2 ml of dichloromethane was stirred at room temperature overnight. The mixture was diluted with 10 ml of dichloromethane, washed with 10 ml of 2M hydrochloric acid and with 10 ml of saturated aqueous sodium bicarbonate solution, dried over magnesium sulphate, filtered and evaporated. 100mg (94%) of 3-(2,6-dichlorophenyl)-7-(cyclohexylmethylamino)-3,4-dihydro-1-phenylpyrimido[4,5-d]pyrimidin-2(1H)-one were isolated as a white foam of melting point 229-233°C.

Example 24

A mixture of 100 mg (0.22 mmol) of 3-(2,6-dichlorophenyl)-7-methanesulphonyl-1-phenyl-3,4-dihydro-1H-pyrimido[4,5-d]pyrimidin-2-one and 320 mg (2.2 mmol) of 1-aminonaphthalene was heated at 130°C for 4 hours. The mixture was left to cool and was then partitioned between 10 ml of ethyl acetate and 2M hydrochloric acid. The insoluble 1-

aminonaphthalene hydrochloride was removed by filtration. The ethyl acetate phase was separated, washed with 10 ml of saturated aqueous sodium bicarbonate solution, dried over magnesium sulphate, filtered and evaporated. The residue was purified by flash column chromatography on silica gel using ethyl acetate/hexane (1:1) for the elution. Product-containing fractions were evaporated to give 46 mg (40%) of 3-(2,6-dichlorophenyl)-3,4-dihydro-7-(1-naphthylamino)-1-phenylpyrimido[4,5-d]pyrimidin-2(1H)-one as a pale pink solid of melting point 213-214°C.

Example 25

A mixture of 100 mg (0.26 mmol) of 3-(2,6-dichlorophenyl)-3,4-dihydro-7-methanesulphonyl-1-methylpyrimido[4,5-d]pyrimidin-2(1H)-one and 136 mg (1 mmol) of p-xylenediamine was heated at 70°C for 20 minutes. The product was purified by flash column chromatography on silica gel using dichloromethane/methanol/water/acetic acid (90:18:3:2) for the elution. Product-containing fractions were combined and evaporated. The residue was dissolved in 20 ml of dichloromethane, washed with 20 ml of saturated aqueous sodium bicarbonate solution, dried over magnesium sulphate, filtered and evaporated to give 35 mg (30%) of 7-[4-(aminomethyl)benzylamino]-3-(2,6-dichlorophenyl)-3,4-dihydro-1-methylpyrimido[4,5-d]pyrimidin-2(1H)-one as a white solid of melting point 151-152°C.

Example 26

A mixture of 100 mg (0.26 mmol) of 3-(2,6-dichlorophenyl)-3,4-dihydro-7-methanesulphonyl-1-methylpyrimido[4,5-d]pyrimidin-2(1H)-one and 140 mg (1 mmol) of 2-(4-aminophenyl)ethylamine was heated at 70°C for 20 minutes. The product was purified by flash column chromatography using 5% methanol in dichloromethane for the elution. Product-containing fractions were combined and evaporated. The residue was recrystallized from ethyl acetate and 3 mg (3%) of 7-[2-(4-aminophenyl)ethylamino]-3-(2,6-dichlorophenyl)-3,4-dihydro-1-methylpyrimido[4,5-d]pyrimidin-2(1H)-one were isolated as a yellow solid of melting point 174-175°C.

Example 27

A mixture of 100 mg (0.26 mmol) of 3-(2,6-dichlorophenyl)-3,4-dihydro-7-methanesulphonyl-1-methylpyrimido[4,5-d]pyrimidin-2(1H)-one and 238 mg (1.07 mmol) of 4-(2-diethylaminoethoxy)benzylamine was heated at 170°C for 30 minutes. The product was purified by flash column chromatography using dichloromethane/ methanol/water/acetic acid (120:14:3:2) for the elution. Product-containing fractions were combined and evaporated to give 40 mg (29%) of 3-(2,6-dichlorophenyl)-7-[4-[2-(diethylamino)ethoxy]benzylamino]-3,4-dihydro-1-methylpyrimido[4,5-d]pyrimidin-2(1H)-one as a white solid of melting point 137-138°C.

The 4-(2-diethylaminoethoxy)benzylamine used as the starting material was prepared as follows:

a) A solution of 8.04 g (67 mmol) of 4-cyanophenol in 100 ml of xylene was treated with a solution of 2.99 g (74 mmol) of sodium hydroxide in 20ml of water and the mixture was stirred for 30 minutes. To this mixture were added 13.88 g (100 mmol) of potassium carbonate and 12.83 g (75 mmol) of 2-diethylaminoethyl chloride hydrochloride. The resulting mixture was then heated at reflux for 3 hours, subsequently left to cool, washed twice with 50 ml of water each time, dried over magnesium sulphate, filtered and evaporated to give 10.93g (74%) of 4-(2-diethylaminoethoxy)benzonitrile as a colourless mobile liquid.

b) A 1M solution of lithium aluminium hydride (5ml; 5mmol) was added dropwise to a stirred solution of 1.01 g (5 mmol) of 4-(2-diethylaminoethoxy)benzonitrile in 5 ml of dry tetrahydrofuran at 0°C. The mixture was warmed to room temperature and stirred overnight. The reaction was quenched by the cautious addition of a saturated solution of 5 ml of Rochelle's salt and then evaporated. The residue was partitioned between 25 ml of diethyl ether and 25 ml of water and the organic phase was separated, dried over magnesium sulphate and evaporated. The crude product was purified by flash column chromatography on silica gel using dichloromethane/methanol/water/acetic acid (60:18:2:3) for the elution. Product-containing fractions were combined and evaporated to give 785mg (71%) of4-(2-diethylaminoethoxy)benzylamine as a colourless oil. Mass spectrum (ESI) $MH^+ = 223$.

Example 28

A mixture of 65 mg (0.19 mmol) of 3-(2,6-dimethylphenyl)-7-methanesulphonyl-3,4-dihydro-1-methylpyrimido[4,5-d]pyrimidin-2(1H)-one and 180 mg (0.87 mmol) of 4-[2-(diethylamino)ethoxy]aniline was heated at 180°C for 30 minutes and then cooled. The residue was subjected to column chromatography on silica gel using dichloromethane/ methanol/acetic acid/water (240:24:3:2) for the elution. Product-containing fractions were combined and evaporated and the residue was evaporated with toluene. The residue was dissolved in 20 ml of dichloromethane, washed three times with 20 ml of saturated aqueous sodium bicarbonate solution each time, dried over magnesium sulphate, filtered and evaporated to give 15mg of a pink oil which was purified by HPLC. The mobile phase was water/0.1% trifluoroacetic acid (A) and acetonitrile/0.07% trifluoroacetic acid (B); the gradient was 5%-95% B over 20 minutes; and the product was detected using an ultraviolet detector at a wavelength of 215 nm. Product-containing fractions were lyophilized and the lyophilizate was dissolved in 20 ml of dichloromethane, washed three times with 20 ml of saturated aqueous sodium bicarbonate solution each time, dried over magnesium sulphate, filtered and evaporated to give 10 mg (11%) of 7-[4-[2-(diethylamino)ethoxy]anilino]-3,4-dihydro-1-methyl-3-(2,6-dimethylphenyl)pyrimido[4,5-d]pyrimidin-2(1H)-one as a white solid of melting point 58°C.

The 3-(2,6-dimethylphenyl)-7-methanesulphonyl-3,4-dihydro-1-methylpyrimido-[4,5-d]pyrimidin-2(1H)-one used as the starting material was prepared as follows:

a) To a mixture of 200 mg (1.1 mmol) of 4-methylamino-2-methylthiopyrimidine-5-carboxaldehyde and 0.15 ml (1.2 mmol) of 2,6-dimethylaniline in 5 ml of dichloromethane were added 350 mg (1.6 mmol) of sodium triacetoxyborohydride and then 0.1 ml (1.7 mmol) of acetic acid. After 5 hours a further 0.15 ml of 2,6-dimethylaniline was added and the mixture was stirred at room temperature for 18 hours. 20 ml of saturated aqueous sodium bicarbonate solution and 25 ml of dichloromethane were added. The phases were separated and the aqueous phase was washed twice with 25 ml of dichloromethane. The combined organic solutions were dried over magnesium sulphate, filtered and evaporated. The residue was subjected to column chromatography on silica gel using diethyl ether/ hexane (1:2) for the elution. Product-containing fractions were combined and evaporated to give 40 mg (13%) of 5-(2,6-dimethylphenyl)aminomethyl-4-methylamino-2-methyl-thiopyrimidine as a white solid [mass spectrum (ESI) $MH^+ = 289$] and 200 mg (65%) of 5-

(2,6-dimethylphenyl)iminomethyl-4-methylamino-2-methylthiopyrimidine as a white solid [mass spectrum (ESI) $MH^+ = 287$].

b) A mixture of 195 mg (0.68 mmol) 5-(2,6-dimethylphenyl)aminomethyl-4-methylamino-2-methylthiopyrimidine and 0.19 ml (1.4 mmol) of triethylamine in 10 ml of dioxan was added dropwise to an ice-cooled solution of 0.085 ml (0.7 mmol) of trichloromethyl chloroformate in 10 ml of dioxan. The mixture was then left to warm to room temperature. After a further 10 minutes the mixture was evaporated. To the residue were added 40 ml of dichloromethane and 40 ml of saturated aqueous sodium bicarbonate. The phases were separated and the dichloromethane phase was dried over magnesium sulphate, filtered and evaporated. The residue was dissolved in 15 ml of pyridine and heated at reflux for 1 hour. The mixture was cooled and evaporated. The residue was partitioned between 20 ml of dichloromethane and 20 ml of 2M hydrochloric acid. The organic phase was washed with 20 ml of water, dried over magnesium sulphate and evaporated to give 100 mg (47%) of 3-(2,6-dimethylphenyl)-7-methylthio-3,4-dihydro-1-methylpyrimido-[4,5-d]pyrimidin-2(1H)-one as an off-white solid. Mass spectrum (ESI) $MH^+ = 315$.

c) A solution of 100 mg (0.32 mmol) of 3-(2,6-dimethylphenyl)-7-methylthio-3,4-dihydro-1-methylpyrimido[4,5-d]pyrimidin-2(1H)-one in 10 ml of dichloromethane was treated with 220 mg (0.64 mmol) of 3-chloroperbenzoic acid (50% w/w in water). After 18 hours 30 ml of saturated aqueous sodium bicarbonate solution and 20 ml of dichloromethane were added and the phases were separated. The organic phase was dried over magnesium sulphate, filtered and evaporated to give 65 mg (59%) of 3-(2,6-dimethylphenyl)-7-methanesulphonyl-3,4-dihydro-1-methylpyrimido[4,5-d]pyrimidin-2(1H)-one as a white solid. Mass spectrum (ESI) $MH^+ = 347$.

Example 29

A mixture of 250 mg (0.67 mmol) of 3-(2,6-dichlorophenyl)-7-methanesulphonyl-3,4-dihydropyrimido[4,5-d]pyrimidin-2(1H)-one and 600 mg (2.9 mmol) of 4-[2-(diethylamino)ethoxy]aniline was heated at 180°C for 35 minutes and then cooled. The residue was subjected to column chromatography on silica gel using dichloromethane/methanol/acetic acid/water 240:24:3:2 for the elution. Product-containing fractions were combined and evaporated and the residue was evaporated with toluene. The residue was dissolved in 30 ml of dichloromethane, washed twice with 20 ml of saturated aqueous sodium bicarbonate solution each time, dried over magnesium sulphate, filtered and

evaporated. The residue was triturated in hexane, filtered off and dried to give 70mg (21%) of 3-(2,6-dichlorophenyl)-7-[4-[2-(diethylamino)ethoxy]anilino]-3,4-dihydropyrimido-[4,5-d]pyrimidin-2(1H)-one as an off-white solid of melting point 248°C.

Example 30

A mixture of 70 mg (0.16 mmol) of 3-(2,6-dichlorophenyl)-1-isopropyl-7-methanesulphonyl-3,4-dihydropyrimido[4,5-d]pyrimidin-2(1H)-one and 166 mg (0.8 mmol) of 4-[2-(diethylamino)ethoxy]aniline was heated at 180°C for 35 minutes and then cooled. The residue was subjected to column chromatography on silica gel using dichloromethane/methanol/acetic acid/water (240:24:3:2) for the elution. Product-containing fractions were combined and evaporated and the residue was evaporated with toluene. The residue was then dissolved in 30 ml of dichloromethane, washed twice with 20 ml of saturated aqueous sodium bicarbonate solution each time, dried over magnesium sulphate, filtered and evaporated to give 5 mg (22%) of 3-(2,6-dichlorophenyl)-7-[4-[2-(diethylamino)ethoxy]anilino]-3,4-dihydro-1-isopropylpyrimido[4,5-d]pyrimidin-2(1H)-one as a white solid of melting point 125°C.

The 3-(2,6-dichlorophenyl)-1-isopropyl-7-methanesulphonyl-3,4-dihydro-pyrimido[4,5-d]pyrimidin-2(1H)-one used as the starting material was prepared as follows:

a) A solution, cooled in ice, of 100 mg (0.27 mmol) of 3-(2,6-dichlorophenyl)-7-methylthio-3,4-dihydropyrimido[4,5-d]pyrimidin-2(1H)-one in 6 ml of dimethyl-formamide was treated with 13 mg (0.33 mmol) of sodium hydride (60% w/w). After 30 minutes the mixture was treated with 0.03 ml (0.3 mmol) of 2-bromopropane and then heated to 90°C for 2 hours, cooled and left to stand for 3 days. The mixture was evaporated and the residue was treated with 30 ml of dichloromethane and 30 ml of water. The phases were separated and the organic phase was washed with 30 ml of water, dried over magnesium sulphate, filtered and evaporated to give 60 mg (54%) of 3-(2,6-dichloro-phenyl)-1-isopropyl-7-methylthio-3,4-dihydropyrimido[4,5-d]pyrimidin-2(1H)-one as a yellow solid. Mass spectrum (ESI) $MH^+ = 383$.

b) A solution of 60 mg (0.16 mmol) of 3-(2,6-dichlorophenyl)-1-isopropyl-7-methyl-thio-3,4-dihydropyrimido[4,5-d]pyrimidin-2(1H)-one in 10 ml of dichloromethane was treated with 108 mg (0.32 mmol) of 3-chloroperbenzoic acid (50% w/w in water) and

stirred for 18 hours. 0.2 ml of dimethyl sulphoxide was added. After a further 15 minutes 15 ml of saturated aqueous sodium bicarbonate solution were added and the phases were separated. The organic phase was washed with 30 ml of saturated aqueous sodium bicarbonate solution, dried over magnesium sulphate and evaporated to give 65 mg (100%) of 3-(2,6-dichlorophenyl)-1-isopropyl-7-methanesulphonyl-3,4-dihydro-pyrimido[4,5-d]pyrimidin-2(1H)-one as a white solid. Mass spectrum (ESI) $MH^+ = 415$.

Example 31

A mixture of 200 mg (0.6 mmol) of 3-(2-methylphenyl)-7-methanesulphonyl-3,4-dihydro-1-methylpyrimido[4,5-d]pyrimidin-2(1H)-one and 300 mg (1.4 mmol) of 4-[2-(diethylamino)ethoxy]aniline was heated at 180°C for 35 minutes and then cooled. The residue was subjected to column chromatography on silica gel using dichloromethane/ methanol/acetic acid/water (240:24:3:2) for the elution. Product-containing fractions were combined and evaporated and the residue was evaporated with toluene. The residue was dissolved in 30 ml of dichloromethane, washed twice with 20 ml of saturated aqueous sodium bicarbonate solution each time, dried over magnesium sulphate, filtered and evaporated to give 30 mg (11%) of 7-[4-[2-(diethylamino)ethoxy]anilino]-3,4-dihydro-1-methyl-3-(2-methylphenyl)pyrimido[4,5-d]pyrimidin-2(1H)-one as a pink solid of melting point 132°C.

The 3-(2-methylphenyl)-7-methanesulphonyl-3,4-dihydro-1-methylpyrimido[4,5-d]pyrimidin-2(1H)-one used as the starting material was prepared as follows:

a) A mixture of 300 mg (1.6 mmol) of 4-methylamino-2-methylthiopyrimidine-5-carboxaldehyde, 0.20 ml (1.8 mmol) of o-toluidine and 59 mg (0.3 mmol) of 4-toluene-sulphonic acid in 50 ml of toluene was heated at reflux with azeotropic removal of water for 18 hours. The mixture was cooled and evaporated. The residue was dissolved in 40 ml of ethanol and heated to 70°C. 300 mg (8 mmol) of sodium borohydride were added cautiously and the mixture was heated at 70°C for 2 hours. A further 300 mg (0.8 mmol) of sodium borohydride were added cautiously and the heating was continued for a further hour. The mixture was cooled and then evaporated. The residue was partitioned between 50 ml of 2M aqueous sodium hydroxide solution and 50 ml of ethyl acetate. The organic phase was dried over magnesium sulphate, filtered and evaporated. The residue was subjected to column chromatography on silica gel using diethyl ether/hexane (1:1) for the elution. Product-containing fractions were combined and evaporated to give 190 mg

(43%) of 5-(2-methylphenyl)aminomethyl-4-methylamino-2-methylthiopyrimidine as a white solid. Mass spectrum (ESI) $MH^+ = 275$.

b) A stirred solution, cooled in ice, of 0.7 ml (1.3 mmol) of phosgene (20% in toluene) in 5 ml of tetrahydrofuran was treated dropwise with a solution containing 189 mg (0.69 mmol) of 5-(2-methylphenyl)aminomethyl-4-methylamino-2-methylthiopyrimidine and 0.2 ml (1.4 mmol) of triethylamine in 5 ml of tetrahydrofuran. The mixture was stirred for 1 hour. To the mixture were added 20 ml of tetrahydrofuran and 20 ml of saturated aqueous ammonium chloride solution. The phases were separated and the organic phase was dried over magnesium sulphate, filtered and evaporated to give 210 mg (100%) of 3-(2-methylphenyl)-7-methylthio-3,4-dihydro-1-methylpyrimido[4,5-d]pyrimidin-2(1H)-one as a cream-coloured solid. Mass spectrum (ESI) $MH^+ = 301$.

c) A solution of 210 mg (0.7 mmol) of 3-(2-methylphenyl)-7-methylthio-3,4-dihydro-1-methylpyrimido[4,5-d]pyrimidin-2(1H)-one in 10 ml of dichloromethane was treated with 482 mg (1.4 mmol) of 3-chloroperbenzoic acid (50% w/w in water). After 18 hours 40 ml of saturated aqueous sodium bicarbonate and 40 ml of dichloromethane were added and the phases were separated. The organic phase was dried over magnesium sulphate, filtered and evaporated to give 200 mg (86%) of 3-(2-methylphenyl)-7-methanesulphonyl-3,4-dihydro-1-methylpyrimido[4,5-d]pyrimidin-2(1H)-one as a white solid. Mass spectrum (ESI) $MH^+ = 333$.

Example 32

A mixture of 40 mg (0.096 mmol) of 3-(2,6-dichlorophenyl)-7-methanesulphonyl-3,4-dihydro-1-phenylpyrimido[4,5-d]pyrimidin-2(1H)-one and 1 ml (11 mmol) of aniline was heated at 180°C for 45 minutes, cooled and partitioned between 30 ml of ethyl acetate and 30 ml of 2M hydrochloric acid. The separated organic phase was dried over magnesium sulphate, filtered and evaporated. The residue was subjected to column chromatography on silica gel using ethyl acetate/hexane (1:2) for the elution. Product-containing fractions were combined and evaporated to give a tan solid which was purified further by HPLC. The mobile phase was water/0.1% trifluoroacetic acid (A) and acetonitrile /0.07% trifluoroacetic acid (B); the gradient was 5%-95% B over 20 minutes; and the product was detected with an ultraviolet detector at a wavelength of 215 nm. The product-containing fraction was lyophilized to give 5 mg (4%) of 7-anilino-3-(2,6-

dichlorophenyl)-3,4-dihydro-1-phenylpyrimido[4,5-d]pyrimidin-2(1H)-one as a white solid of melting point 138°C.

Example 33

A mixture of 56 mg (0.13 mmol) of 3-(2,6-dichlorophenyl)-7-methanesulphonyl-3,4-dihydro-1-phenylpyrimido[4,5-d]pyrimidin-2(1H)-one and 1 ml of 4-methoxybenzylamine was heated at 100°C for 30 minutes, then cooled and partitioned between 30 ml of dichloromethane and 30 ml of 2M hydrochloric acid. The organic phase was dried over magnesium sulphate, filtered and evaporated to give 68 mg (100%) of 3-(2,6-dichlorophenyl)-3,4-dihydro-7-(4-methoxybenzyl)amino-1-phenylpyrimido[4,5-d]-pyrimidin-2(1H)-one as a yellow solid of melting point 56°C.

Example 34

A solution of 40 mg (0.96 mmol) of 3-(2,6-dichlorophenyl)-7-(4-methoxybenzyl)-amino-3,4-dihydro-1-phenylpyrimido[4,5-d]pyrimidin-2(1H)-one in 5 ml of trifluoroacetic acid was heated at reflux for 5 hours. The mixture was evaporated and the residue was partitioned between 30 ml of ethyl acetate and 30 ml of 2M aqueous sodium hydroxide. The organic phase was dried over magnesium sulphate, filtered and evaporated and the residue was subjected to column chromatography on silica gel using dichloromethane/methanol (20:1) for the elution. Product-containing fractions were combined and evaporated to give 10 mg (27%) of 7-amino-3-(2,6-dichlorophenyl)-3,4-dihydro-1-phenylpyrimido[4,5-d]pyrimidin-2(1H)-one as a white solid of melting point >300°C.

Example 35

A mixture of 200 mg (0.56 mmol) of 3-(2,6-difluorophenyl)-7-methanesulphonyl-3,4-dihydro-1-methylpyrimido[4,5-d]pyrimidin-2(1H)-one and 400 mg (1.9 mmol) of 4-[2-(diethylamino)ethoxy]aniline was heated at 180°C for 30 minutes and then cooled. The residue was subjected to column chromatography on silica gel using dichloromethane/methanol/acetic acid/water (240:24:3:2) for the elution. Product-containing fractions were combined and evaporated and the residue was evaporated with toluene. The residue was then dissolved in 40 ml of dichloromethane, washed with 40 ml of saturated aqueous sodium bicarbonate solution, dried over magnesium sulphate, filtered and evaporated to

give 30 mg (11%) of 7-[4-[2-(diethylamino)ethoxy]anilino]-3-(2,6-difluorophenyl)-3,4-dihydro-1-methylpyrimido[4,5-d]pyrimidin-2(1H)-one as an orange coloured solid. Mass spectrum (ESI) $MH^+ = 483$.

The 3-(2,6-difluorophenyl)-7-methanesulphonyl-3,4-dihydro-1-methylpyrimido-[4,5-d]pyrimidin-2(1H)-one used as the starting material was prepared as follows:

a) A mixture of 300 mg (1.6 mmol) of 4-methylamino-2-methylthiopyrimidine-5-carboxaldehyde, 232 mg (1.8 mmol) of 2,6-difluoroaniline and 59 mg (0.3 mmol) of 4-toluenesulphonic acid monohydrate in 30 ml of toluene was heated at reflux with azeotropic removal of water for 18 hours. The mixture was cooled and evaporated. The residue was dissolved in 20 ml of tetrahydrofuran and added dropwise to a solution of 1.6 ml (1.6 mmol) of lithium aluminium hydride (1M in tetrahydrofuran) in a further 20ml of tetrahydrofuran. After 30 minutes the mixture was cooled in ice and 0.5 ml of water, 0.75 ml of 2M sodium hydroxide solution and finally 1 ml of water were cautiously added dropwise. The resulting suspension was filtered through a filter aid and the filtrate was evaporated. The residue was subjected to column chromatography on silica gel using diethyl ether/hexane (1:1) for the elution to yield 210 mg (44%) of 5-(2,6-difluoro-phenyl)aminomethyl-4-methylamino-2-methylthiopyrimidine as a white solid. Mass spectrum (ESI) $MH^+ = 297$.

b) A stirred solution, cooled in ice, of 0.7 ml (1.3 mmol) of phosgene (20% in toluene) in 5 ml of tetrahydrofuran was treated dropwise with a solution of 210 mg (0.71 mmol) of 5-(2,6-difluorophenyl)aminomethyl-4-methylamino-2-methylthiopyrimidine and 0.2 ml (1.4 mmol) of triethylamine in 5 ml or tetrahydrofuran. The mixture was stirred for 1 hour. To the mixture were added 20 ml of tetrahydrofuran and 20 ml of saturated aqueous ammonium chloride solution and the phases were separated. The organic phase was dried over magnesium sulphate, filtered and evaporated to give 200 mg (87%) of 3-(2,6-difluorophenyl)-7-methylthio-3,4-dihydro-1-methylpyrimido[4,5-d]pyrimidin-2(1H)-one as a white solid. Mass spectrum (ESI) $MH^+ = 323$.

c) A solution of 200 mg (0.62 mmol) of 3-(2,6-difluorophenyl)-7-methylthio-3,4-dihydro-1-methylpyrimido[4,5-d]pyrimidin-2(1H)-one in 10 ml of dichloromethane was treated with 430 mg (1.24 mmol) of 3-chloroperbenzoic acid (50% w/w water). After 18 hours 40 ml of saturated aqueous sodium bicarbonate solution and 40 ml of dichloro-methane were added and the phases were separated. The organic phase was dried over

magnesium sulphate, filtered and evaporated to give 200 mg (91%) of 3-(2,6-difluorophenyl)-7-methanesulphonyl-3,4-dihydro-1-methylpyrimido[4,5-d]pyrimidin-2(1H)-one as a white solid Mass spectrum (ESI) $MH^+ = 355$.

Example 36

A mixture of 200 mg (0.52 mmol) of 3-(2,4-dichlorophenyl)-7-methanesulphonyl-3,4-dihydro-1-methylpyrimido[4,5-d]pyrimidin-2(1H)-one and 300 mg (1.4 mmol) of 4-[2-(diethylamino)ethoxy]aniline was heated at 180°C for 30 minutes and then cooled. The residue was subjected to column chromatography on silica gel using dichloromethane/methanol/acetic acid/water (240:24:3:2) for the elution. Product-containing fractions were combined and evaporated and the residue was evaporated with toluene. The residue was then dissolved in 40 ml of dichloromethane, washed with 40 ml of saturated aqueous sodium bicarbonate solution, dried over magnesium sulphate, filtered and evaporated to give 20 mg (8%) of 3-(2,4-dichlorophenyl)-7-[4-[2-(diethylamino)ethoxy]anilino]-3,4-dihydro-1-methylpyrimido[4,5-d]pyrimidin-2(1H)-one as an orange coloured solid of melting point 172°C.

The 3-(2,4-dichlorophenyl)-7-methanesulphonyl-3,4-dihydro-1-methylpyrimido-[4,5-d]pyrimidin-2(1H)-one used as the starting material was prepared in a manner analogous to that described in Example 35 for 3-(2,6-difluorophenyl)-7-methanesulphonyl-3,4-dihydro-1-methylpyrimido[4,5-d]pyrimidin-2(1H)-one using 2,4-dichloroaniline in place of 2,6-difluoroaniline.

Example 37

A mixture of 200 mg (0.52 mmol) of 3-(2,6-dichlorophenyl)-7-methanesulphonyl-3,4-dihydro-1-[3-(2-phthalimidoethyl)phenyl]pyrimido[4,5-d]pyrimidin-2(1H)-one and 3 ml of aniline was heated at 180°C for 40 minutes and then cooled. The mixture was partitioned between 40 ml of dichloromethane and 40 ml of 2M hydrochloric acid. The organic phase was dried over magnesium sulphate, filtered and evaporated. The residue was subjected to column chromatography on silica gel using diethyl ether/hexane (1:1) for the elution. The product-containing fractions were combined and evaporated to give 30 mg (29%) of 7-anilino 3-(2,6-dichlorophenyl)-3,4-dihydro-1-[3-(2-

phthalimidoethyl)phenyl]pyrimido[4,5-d]pyrimidin-2(1H)-one as a white solid of melting point 142°C.

The 3-(2,6-dichlorophenyl)-7-methanesulphonyl-3,4-dihydro-1-[3-(2-phthalimidoethyl)phenyl]pyrimido[4,5-d]pyrimidin-2(1H)-one used as the starting material was prepared as follows:

a) To a solution of 10 g (60 mmol) of 3-nitrophenylacetic acid in 120 ml of ethanol were added 20 ml of a saturated solution of hydrogen chloride in ethyl acetate and the mixture was heated at reflux for 4 hours, cooled and left to stand at room temperature for 18 hours. The mixture was evaporated and the residue was partitioned between 120 ml of diethyl ether and 100 ml of saturated aqueous sodium bicarbonate solution. The organic phase was dried over magnesium sulphate, filtered and evaporated to give 10.3g (82%) of ethyl 3-nitrophenylacetate as a pale yellow oil. [NMR spectrum (250MHz) δ1.25(t) (3H), δ3.68(s) (2H), δ4.16(q) (2H), δ6.5-δ6.7(m) (3H), δ7.09(dd) (1H)].

b) A solution of 10.3 g (49 mmol) of ethyl 3-nitrophenylacetate in 120 ml of ethanol was hydrogenated over 1 g of 10% palladium on charcoal for 6 hours. The mixture was filtered and the filtrate evaporated to give 9.3g (100%) of ethyl 3-aminophenylacetate as a yellow oil. [NMR spectrum (250MHz) δ1.19(t) (3H), δ3.48(s) (2H), δ4.16(q) (2H), δ7.48(dd) (1H), δ7.62(d) (1H), δ8.12(m) (2H)].

c) A mixture of 5 g (21.5 mmol) of ethyl 4-chloro-2-methylthio-pyrimidine-5-carboxylate and 4 g (22.3 mmol) of ethyl 3-aminophenylacetate in 80 ml of 1,4-dioxan was treated with 6 ml (43 mmol) of triethylamine and then heated at 60°C for 4 hours. The mixture was cooled and evaporated. The residue was partitioned between 120 ml of ethyl acetate and 100 ml of 2M hydrochloric acid. The organic phase was dried over magnesium sulphate, filtered and evaporated to give 7.4 g (92%) of ethyl 4-[3-(ethoxycarbonylmethyl)-phenyl]amino-2-methylthiopyrimidine-5-carboxylate as a pale orange coloured oil which solidifies slowly to a white solid. [Mass spectrum (ESI) MH^+ = 376].

d) To a solution, cooled in ice, of 1.3 g (34 mmol) of lithium aluminium hydride in 70 ml of tetrahydrofuran was added dropwise a solution of 6.5 g (17 mmol) of ethyl 4-[3-(ethoxycarbonylmethyl)phenyl]amino-2-methylthiopyrimidine-5-carboxylate in 70ml of tetrahydrofuran. The cooling was removed and the mixture was stirred at room temper-

ature for 2 hours. The reaction was quenched by the cautious dropwise addition of 1.2 ml of water, 1.2 ml of 2M aqueous sodium hydroxide and finally 3.6 ml of water. The resulting suspension was filtered through a filter aid and the filtrate was evaporated. The residue was subjected to column chromatography on silica gel using dichloromethane/methanol (10:1) for the elution. Product-containing fractions were combined and evaporated to give 3.1 g (62%) of 5-hydroxymethyl-4-[3-(2-hydroxyethyl)phenyl]amino-2-methylthiopyrimidine as a yellow oil. Mass spectrum (ESI) $MH^+ = 292$.

e) To a solution of 3.1 g (10.7 mmol) of 5-hydroxymethyl-4-[3-(2-hydroxyethyl)-phenyl]amino-2-methylthiopyrimidine in 250 ml of dichloromethane were added 9 g (100 mmol) of manganese dioxide and the mixture was stirred for 24 hours. The mixture was filtered through a filter aid and the filtrate was evaporated to give 2.6 g (84%) of 5-formyl-4-(3-(2-hydroxyethyl)phenylamino-2-methylthiopyrimidine as a white solid. Mass spectrum (ESI) $MH^+ = 290$.

f) A solution of 4 g (13.8 mmol) of 5-formyl-4-[3-(2-hydroxyethyl)phenyl]amino-2-methylthiopyrimidine in 80 ml of toluene was treated with 2.4 g (15 mmol) of 2,6-dichloroaniline and 0.25 g (1.3 mmol) of 4-toluenesulphonic acid monohydrate and the mixture was heated under reflux with azeotropic removal of water for 18 hours and then cooled. The mixture was evaporated and the residue was dissolved in 40 ml of tetrahydrofuran and added dropwise to a solution of 0.6 g (16 mmol) of lithium aluminium hydride in 40 ml of tetrahydrofuran. After 1 hour the reaction was quenched by the cautious dropwise addition of 0.6 ml of water, 0.6 ml of 2M aqueous sodium hydroxide and 1.8 ml of water. The resulting suspension was filtered through a filter aid and the filtrate was evaporated. The residue was subjected to column chromatography on silica using dichloromethane/methanol for the elution in a gradient from a ratio of 50:1 to a ratio of 10:1. Product-containing fractions from the first product to be eluted from the column were combined and evaporated to give 1 g (17%) of 5-(2,6-dichloroanilino)methyl-4-[3-(2-hydroxyethyl)phenyl]amino-2-methylthiopyrimidine as a white solid. Mass spectrum (ESI) $MH^+ = 435$. Product-containing fractions from the second product to be eluted from the column were combined and evaporated to give 1.8 g (45%) of 5-hydroxymethyl-4-[3-(2-hydroxyethyl)phenyl]amino-2-methylthiopyrimidine as a white solid. Mass spectrum (ESI) $MH^+ = 292$.

g) A solution of 1 g (2.3 mmol) of 5-(2,6-dichloroanilino)methyl-4-[3-(2-hydroxy-ethyl)phenyl]amino-2-methylthiopyrimidine in 60 ml of tetrahydrofuran was treated with

0.8 ml (6 mmol) of triethylamine and the mixture was added dropwise to a solution of 1.8 ml of phosgene (20% in toluene) in 40 ml of tetrahydrofuran. The cooling was removed. After 2 hours 100 ml of saturated aqueous ammonium chloride solution were added. The mixture was separated and the organic phase was dried over magnesium sulphate, filtered and evaporated. The residue was subjected to column chromatography on silica gel using diethyl ether/hexane (1:2) for the elution. Product-containing fractions were combined and evaporated to give 0.5 g (50%) of 3-(2,6-dichlorophenyl)-7-methylthio-3,4-dihydro-1-[3-(2-chloroethyl)phenyl]pyrimido[4,5-d]pyrimidin-2(1H)-one as a white solid Mass spectrum (ESI) $MH^+ = 479$.

h) A solution of 0.5 g (1.1 mmol) of 3-(2,6-dichlorophenyl)-7-methylthio-3,4-dihydro-1-(3-(2-chloroethyl)phenyl)pyrimido[4,5-d]pyrimidin-2(1H)-one in 30 ml of dimethylformamide was treated with 0.2 g (1.1 mmol) of phthalimide potassium salt and the mixture was heated at 80°C for 2 hours. The cooled mixture was evaporated and partitioned between 40 ml of dichloromethane and 40 ml of water. The organic phase was dried over magnesium sulphate, filtered and evaporated. The residue was subjected to column chromatography on silica gel using diethyl ether/hexane (1:1) for the elution. Product-containing fractions were combined and evaporated to give 0.43 g (70%) of 3-(2,6-dichlorophenyl)-7-methylthio-3,4-dihydro-1-[3-(2-phthalimidoethyl)phenyl]-pyrimido[4,5-d]pyrimidin-2(1H)-one as a white solid. Mass spectrum (ESI) $MH^+ = 590$.

i) A solution of 400 mg (0.68 mmol) of 3-(2,6-dichlorophenyl)-7-methylthio-3,4-dihydro-1-[3-(2-phthalimidoethyl)phenyl]pyrimido[4,5-d]pyrimidin-2(1H)-one in 20 ml of dichloromethane was treated with 470 mg (1.36 mmol) of 3-chloroperbenzoic acid (50% w/w in water). After 18 hours 40 ml of saturated aqueous sodium bicarbonate solution and 40 ml of dichloromethane were added and the phases were separated. The organic phase was dried over magnesium sulphate, filtered and evaporated to give 370 mg (88%) of 3-(2,6-dichlorophenyl)-7-methanesulphonyl-3,4-dihydro-1-[3-(2-phthalimido-ethyl)phenyl]pyrimido[4,5-d]pyrimidin-2(1H)-one as a white solid. Mass spectrum (ESI) $MH^+ = 622$.

Example 38

A solution of 30 mg (0.05 mmol) of 3-(2,6-dichlorophenyl)-7-anilino-3,4-dihydro-1-[3-(2-phthalimidoethyl)phenyl]pyrimido[4,5-d]pyrimidin-2(1H)-one in 5ml of ethanol was treated with 0.02 ml of hydrazine hydrate. After 5 hours the mixture was evaporated

and 10 ml of dichloromethane were added to the residue. The resulting suspension was filtered and the filtrate was evaporated. The residue was subjected to column chromatography on silica gel using dichloromethane/methanol/acetic acid/water (240:24:3:2) for the elution. Product-containing fractions were combined and evaporated and the residue was evaporated with toluene. The residue was then dissolved in 40 ml of dichloromethane, washed with 40 ml of saturated aqueous sodium bicarbonate solution, dried over magnesium sulphate, filtered and evaporated to give 12 mg (50%) of 1-[3-(2-aminoethyl)-phenyl]-7-anilino-3-(2,6-dichlorophenyl)-3,4-dihydropyrimido[4,5-d]pyrimidin-2(1H)-one as a white solid of melting point 208°C.

Example 39

A mixture of 250 mg (0.98 mmol) of 3-methyl-7-methanesulphonyl-3,4-dihydro-1-methylpyrimido[4,5-d]pyrimidin-2(1H)-one and 560 mg (2.7 mmol) of 4-[2-(diethylamino)ethoxy]aniline was heated at 180°C for 35 minutes and then cooled. The residue was subjected to column chromatography on silica gel using dichloromethane/methanol/acetic acid/water (240:24:3:2) for the elution. Product-containing fractions were combined and evaporated and the residue was evaporated with toluene. The residue was then dissolved in 40 ml of dichloromethane, washed with 40 ml of saturated aqueous sodium bicarbonate solution, dried over magnesium sulphate, filtered and evaporated. The residue was triturated in hexane, filtered off and dried to give 23 mg (7%) of 7-[4-[2-(diethylamino)ethoxy]anilino]-3,4-dihydro-1,3-dimethylpyrimido[4,5-d]pyrimidin-2(1H)-one as a white solid of melting point 186°C.

The 3-methyl-7-methanesulphonyl-3,4-dihydro-1-methylpyrimido-[4,5-d]pyrimidin-2(1H)-one used as the starting material was prepared in a manner analogous to that described in Example 4 for 3-cyclohexyl-7-methanesulphonyl-3,4-dihydro-1-methylpyrimido[4,5-d]pyrimidin-2(1H)-one using methylamine (as a 2M solution in tetrahydrofuran) in place of cyclohexylamine.

Example 40

A mixture of 160 mg (0.45 mmol) of 3-(2-chloro-6-methylphenyl)-7-methanesulphonyl-3,4-dihydro-1-methylpyrimido[4,5-d]pyrimidin-2(1H)-one and 300 mg (1.4 mmol) of 4-[2-(diethylamino)ethoxy]aniline was heated at 180°C for 35 minutes and then cooled. The residue was subjected to column chromatography on

silica gel using dichloromethane/methanol/acetic acid/water (240:24:3:2) for the elution. Product-containing fractions were combined and evaporated and the residue was evaporated with toluene. The residue was then dissolved in 30 ml of dichloromethane, washed twice with 20 ml of saturated aqueous sodium bicarbonate solution each time, dried over magnesium sulphate, filtered and evaporated. The residue was purified further by HPLC. The mobile phase was water/0.1% trifluoroacetic acid (A) and acetonitrile /0.07% trifluoroacetic acid (B); the gradient was 5%-95% B over 20 minutes; and the product was detected using an ultraviolet detector at a wavelength of 215 nm. Product-containing fractions were lyophilized and the lyophilizate was dissolved in 30 ml of dichloromethane, washed twice with 20 ml of saturated aqueous sodium bicarbonate solution each time, dried over magnesium sulphate, filtered and evaporated to give 5 mg (2%) of 3-(2-chloro-6-methylphenyl)-7-[4-[2-(diethylamino)ethoxy]anilino]-3,4-dihydro-1-methylpyrimido[4,5-d]pyrimidin-2(1H)-one as a yellow gum. Mass spectrum (ESI) $MH^+ = 495$.

The 3-(2-chloro-6-methylphenyl)-7-methanesulphonyl-3,4-dihydro-1-methylpyrimido[4,5-d]pyrimidin-2(1H)-one used as the starting material was prepared in a manner analogous to that described in Example 35 for 3-(2,6-difluorophenyl)-7-methanesulphonyl-3,4-dihydro-1-methylpyrimido[4,5-d]pyrimidin-2(1H)-one using 2-chloro-6-methylaniline in place of 2,6-difluoroaniline.

Example 41

A mixture of 350 mg (1.2 mmol) of 3-isopropyl-7-methanesulphonyl-3,4-dihydro-1-methylpyrimido[4,5-d]pyrimidin-2(1H)-one and 500 mg (2.4 mmol) of 4-[2-(diethylamino)ethoxy]aniline was heated at 180°C for 35 minutes and then cooled. The residue was subjected to column chromatography on silica gel using dichloromethane/methanol/acetic acid/water (240:24:3:2) for the elution. Product-containing fractions were combined and evaporated and the residue was evaporated with toluene. The residue was then dissolved in 40 ml of dichloromethane, washed with 40 ml of saturated aqueous sodium bicarbonate solution, dried over magnesium sulphate, filtered and evaporated. The residue was triturated in hexane, filtered off and dried to give 40 mg (8%) of 7-[4-[2-(diethylamino)ethoxy]anilino]-3,4-dihydro-3-isopropyl-1-methylpyrimido[4,5-d]pyrimidin-2(1H)-one as a white solid of melting point 154°C.

The 3-isopropyl-7-methanesulphonyl-3,4-dihydro-1-methylpyrimido[4,5-d]pyrimidin-2(1H)-one used as the starting material was prepared in a manner analogous to that described in Example 4 for 3-cyclohexyl-7-methanesulphonyl-3,4-dihydro-1-methylpyrimido[4,5-d]pyrimidin-2(1H)-one using isopropylamine in place of cyclohexylamine.

Example 42

A mixture of 70 mg (0.15 mmol) of 3-(2,6-dichlorophenyl)-1-[2-cyclohexen-1(RS)-yl]-7-methanesulphonyl-3,4-dihydropyrimido[4,5-d]pyrimidin-2(1H)-one and 150 mg (0.7 mmol) of 4-[2-(diethylamino)ethoxy]aniline was heated at 180°C for 35 minutes and then cooled. The residue was subjected to column chromatography on silica gel using dichloromethane/methanol/acetic acid/water (240:24:3:2) for the elution. Product-containing fractions were combined and evaporated and the residue was evaporated with toluene. The residue was then dissolved in 30 ml of dichloromethane, washed twice with 20 ml of saturated aqueous sodium bicarbonate solution each time, dried over magnesium sulphate, filtered and evaporated to give 5 mg (22%) of 3-(2,6-dichlorophenyl)-1-[2-cyclohexen-1(RS)-yl]-7-[4-[2-(diethylamino)ethoxy]anilino]-3,4-dihydropyrimido[4,5-d]pyrimidin-2(1H)-one as an orange coloured gum. Mass spectrum (ESI) $MH^+ = 581$.

The 3-(2,6-dichlorophenyl)-1-[2-cyclohexen-1(RS)-yl]-7-methanesulphonyl-3,4-dihydropyrimido[4,5-d]pyrimidin-2(1H)-one used as the starting material was prepared as follows:

A solution, cooled in ice, of 200 mg (0.54 mmol) of 3-(2,6-dichlorophenyl)-7-methanesulphonyl-3,4-dihydropyrimido[4,5-d]pyrimidin-2(1H)-one in 12ml of dimethylformamide was treated with 22 mg (0.54 mmol) of sodium hydride (60% w/w). After 30 minutes the mixture was treated with 0.07 ml (0.6 mmol) of 3-bromocyclohexene and then heated at reflux for 4 hours. The mixture was evaporated and 30 ml of dichloromethane and 30 ml of water were added to the residue. The phases were separated and the organic phase was washed with 30 ml of water, dried over magnesium sulphate, filtered and evaporated to give 70 mg (29%) 3-(2,6-dichlorophenyl)-1-[2-cyclohexen-1(RS)-yl]-7-methanesulphonyl-3,4-dihydropyrimido[4,5-d]pyrimidin-2(1H)-one as a brown oil. Mass spectrum (ESI) $MH^+ = 453$.

Example 43

A mixture of 200 mg (0.5 mmol) of 3-(2-bromophenyl)-7-methanesulphonyl-3,4-dihydro-1-methylpyrimido[4,5-d]pyrimidin-2(1H)-one and 208 mg (1 mmol) of 4-[2-(diethylamino)ethoxy]aniline was heated at 180°C for 30 minutes and then cooled. The residue was subjected to column chromatography on silica gel using dichloromethane/methanol/acetic acid/water (240:24:3:2) for the elution. Product-containing fractions were combined and evaporated and the residue was evaporated with toluene. The residue was then dissolved in 40 ml of dichloromethane, washed with 40 ml of saturated aqueous sodium bicarbonate solution, dried over magnesium sulphate, filtered and evaporated to give 22 mg (8%) of 3-(2-bromophenyl)-7-[4-[2-(diethylamino)ethoxy]anilino]-3,4-dihydro-1-methylpyrimido[4,5-d]pyrimidin-2(1H)-one as a cream coloured solid of melting point 144°C.

The 3-(2-bromophenyl)-7-methanesulphonyl-3,4-dihydro-1-methylpyrimido[4,5-d]pyrimidin-2(1H)-one used as the starting material was prepared in a manner analogous to that described in Example 35 for 3-(2,6-difluorophenyl)-7-methanesulphonyl-3,4-dihydro-1-methylpyrimido[4,5-d]pyrimidin-2(1H)-one using 2-bromoaniline in place of 2,6-difluoroaniline.

Example 44

A mixture of 200mg (0.52 mmol) of 3-(2,5-dichlorophenyl)-7-methanesulphonyl-3,4-dihydro-1-methylpyrimido[4,5-d]pyrimidin-2(1H)-one and 218mg (1.04 mmol) of 4-(2-(diethylamino)ethoxy)aniline was heated at 180°C for 30 minutes and then cooled. The residue was subjected to column chromatography on silica gel eluted with dichloromethane:methanol:acetic acid:water in a ratio of 240:24:3:2. Product containing fractions were combined, evaporated and the residue re-evaporated with toluene. The residue was dissolved in dichloromethane (40ml), washed with saturated aqueous sodium bicarbonate (40ml), dried over magnesium sulphate, filtered and evaporated to give 15mg (6%) of 3-(2,5-dichlorophenyl)-7-[4-[2-(diethylamino)ethoxy]anilino]-3,4-dihydro-1-methylpyrimido[4,5-d]pyrimidin-2(1H)-one as a white solid of melting point 138°C [Mass spectrum (ESI) $MH^+ = 514$].

The 3-(2,5-dichlorophenyl)-7-methanesulphonyl-3,4-dihydro-1-methyl-pyrimido[4,5-d]pyrimidin-2(1H)-one used as the starting material was prepared in a manner analogous to that described in Example 35 for 3-(2,6-difluorophenyl)-7-methanesulphonyl-3,4-dihydro-1-methylpyrimido[4,5-d]pyrimidin-2(1H)-one using 2,5-dichloroaniline in place of 2,6-difluoroaniline.

Example 45

A mixture of 200 mg (0.5 mmol) of 3-(3-bromophenyl)-7-methanesulphonyl-3,4-dihydro-1-methylpyrimido[4,5-d]pyrimidin-2(1H)-one and 300 mg (1.4 mmol) of 4-[2-(diethylamino)ethoxy]aniline was heated at 180°C for 35 minutes and then cooled. The residue was subjected to column chromatography on silica gel dichloromethane/methanol/acetic acid/water (240:24:3:2) for the elution. Product-containing fractions were combined, and evaporated and the residue was evaporated with toluene. The residue was then dissolved in 40 ml of dichloromethane, washed with 40 ml of saturated aqueous sodium bicarbonate solution, dried over magnesium sulphate, filtered and evaporated to give 30 mg (11%) of 3-(3-bromophenyl)-7-[4-[2-(diethylamino)ethoxy]anilino]-3,4-dihydro-1-methylpyrimido[4,5-d]pyrimidin-2(1H)-one as an off-white solid of melting point 150°C.

The 3-(3-bromophenyl)-7-methanesulphonyl-3,4-dihydro-1-methylpyrimido[4,5-d]pyrimidin-2(1H)-one used as the starting material was prepared in a manner analogous to that described in Example 35 for 3-(2,6-difluorophenyl)-7-methanesulphonyl-3,4-dihydro-1-methylpyrimido[4,5-d]pyrimidin-2(1H)-one using 3-bromoaniline in place of 2,6-difluoroaniline.

Example 46

A mixture of 380 mg (1.1 mmol) of 3-(2-methoxyphenyl)-7-methanesulphonyl-3,4-dihydro-1-methylpyrimido[4,5-d]pyrimidin-2(1H)-one and 3 ml of aniline was heated at 180°C for 45 minutes, then cooled and partitioned between 30 ml of dichloromethane and 30 ml of 2M hydrochloric acid. The organic phase was dried over magnesium sulphate, filtered and evaporated. The residue was subjected to column chromatography on silica gel using dichloromethane/methanol for the elution in a gradient from a ratio of 99:1 to a ratio of 20:1. Product-containing fractions were combined and evaporated to 7-anilino-

3,4-dihydro-3-(2-methoxyphenyl)-1-methylpyrimido[4,5-d]pyrimidin-2(1H)-one as an off-white solid of melting point 225°C.

The 3-(2-methoxyphenyl)-7-methanesulphonyl-3,4-dihydro-1-methylpyrimido-[4,5-d]pyrimidin-2(1H)-one used as the starting material was prepared in a manner analogous to that described in Example 35 for 3-(2,6-difluorophenyl)-7-methanesulphonyl-3,4-dihydro-1-methylpyrimido[4,5-d]pyrimidin-2(1H)-one using 2-methoxyaniline in place of 2,6-difluoroaniline.

Example 47

A solution of 50 mg (0.14 mmol) of 3-(2-methoxyphenyl)-7-anilino-3,4-dihydro-1-methylpyrimido[4,5-d]pyrimidin-2(1H)-one in 15 ml of 48% aqueous hydrobromic acid was heated at reflux for 1 hour. The mixture was cooled and evaporated and the residue was triturated in hexane. The resultant solid was filtered off and dried to give 40 mg (82%) of 7-anilino-3,4-dihydro-3-(2-hydroxyphenyl)-1-methylpyrimido[4,5-d]pyrimidin-2(1H)-one as an off-white solid of melting point 192°C.

Example 48

A mixture of 200 mg (0.55 mmol) of 3-(4-methoxybenzyl)-7-methanesulphonyl-3,4-dihydro-1-methylpyrimido[4,5-d]pyrimidin-2(1H)-one and 300 mg (1.4 mmol) of 4-[2-(diethylamino)ethoxy]aniline was heated at 180°C for 20 minutes and then cooled. The residue was subjected to column chromatography on silica gel using dichloromethane/methanol/acetic acid/water (240:24:3:2) for the elution. Product-containing fractions were combined, evaporated and the residue was evaporated with toluene. The residue was then dissolved in 40 ml of dichloromethane, washed with 40 ml of saturated aqueous sodium bicarbonate solution, dried over magnesium sulphate, filtered and evaporated. The residue was triturated in hexane, filtered off and dried to give 20 mg (7%) of 7-[4-[2-(diethylamino)ethoxy]anilino]-3,4-dihydro-3-(4-methoxybenzyl)-1-methylpyrimido[4,5-d]-pyrimidin-2(1H)-one as a white solid of melting point 112°C.

The 3-(4-methoxybenzyl)-7-methanesulphonyl-3,4-dihydro-1-methylpyrimido-[4,5-d]pyrimidin-2(1H)-one used as the starting material was prepared in a manner analogous to that described in Example 4 for 3-cyclohexyl-7-methanesulphonyl-3,4-

dihydro-1-methylpyrimido[4,5-d]pyrimidin-2(1H)-one using 4 using 4-methoxybenzylamine in place of cyclohexylamine.

Example 49

A mixture of 300 mg (0.6 mmol) of 3-(2-bromophenyl)-7-methanesulphonyl -3,4-dihydro-1-[3-(2-hydroxyethyl)phenyl]pyrimido[4,5-d]pyrimidin-2(1H)-one and 1.5 ml of 4-methoxybenzylamine was heated at 100°C for 1 hour. The mixture was cooled and partitioned between 30 ml of dichloromethane and 30 ml of 2M aqueous hydrochloric acid. The organic phase was dried over magnesium sulphate, filtered and evaporated. The residue was dissolved in 10 ml of trifluoroacetic acid and then heated at reflux for 3 hours. The mixture was cooled and evaporated and the residue was partitioned between 25 ml of ethyl acetate and 25 ml of saturated sodium bicarbonate solution. The organic phase was dried over magnesium sulphate, filtered and evaporated and the residue was subjected to column chromatography on silica gel using ethyl acetate for the elution. Product-containing fractions were combined and evaporated to give 105 mg (40%) of 7-amino-3-(2-bromophenyl)-3,4-dihydro-1-[3-(2-hydroxyethyl)phenyl]pyrimido[4,5-d]pyrimidin-2(1H)-one as a white solid of melting point 154°C.

The 3-(2-bromophenyl)-7-methanesulphonyl -3,4-dihydro-1-(3-(2-hydroxyethyl)-phenyl)pyrimido[4,5-d]pyrimidin-2(1H)-one used as the starting material was prepared as follows:

a) A solution of 2.5 g (8.65 mmol) of 5-formyl-4-[3-(2-hydroxyethyl)phenyl]amino-2-methylthiopyrimidine in 120 ml of toluene was treated with 1.5 g (9.3mmol) of 2-bromoaniline and 100 mg (0.5 mmol) of 4-toluenesulphonic acid monohydrate and then heated at reflux with azeotropic removal of water for 1 hour. The cooled mixture was evaporated and the residue was dissolved in 4 ml of tetrahydrofuran. The solution obtained was added dropwise to a solution of 9 ml (9 mmol) of lithium aluminium hydride (as a 1M solution in tetrahydrofuran) in 40 ml of tetrahydrofuran. After 1 hour the reaction was quenched by the cautious dropwise addition of 0.35 ml of water, 0.35 ml of 2M aqueous sodium hydroxide and 1 ml of water. The resulting suspension was filtered through a filter aid and the filtrate was evaporated. The residue was partitioned between 150 ml of ethyl acetate and 50 ml of saturated aqueous sodium bicarbonate solution. The organic phase was dried over magnesium sulphate, filtered and evaporated to give 3.5 g

(91%) of 5-(2-bromoanilino)methyl-4-[3-(2-hydroxyethyl)phenyl]amino-2-methylthiopyrimidine as an orange coloured gum. Mass spectrum (ESI) MH^+ = 444, 446.

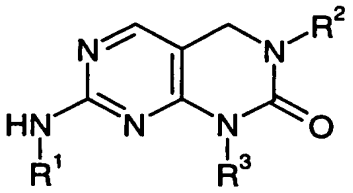
b) A solution of 3.5 g (7.9 mmol) of 5-(2-bromoanilino)methyl-4-[3-(2-hydroxyethyl)phenyl]amino-2-methylthiopyrimidine in 100 ml of dichloromethane was treated with 3.3 g (39 mmol) of dihydropyran and 15 mg (0.08 mmol) of 4-toluenesulphonic acid monohydrate. After 18 hours the mixture was treated with 100 mg (0.4 mmol) of pyridinium 4-toluenesulphonate. After a further 3 days 100 ml of ether and 100 ml of 50% saturated brine were added. The organic phase was dried over magnesium sulphate, filtered and evaporated to give 2.6 g (62%) of 5-(2-bromoanilino)methyl-4-[3-(2-(tetrahydropyran-2-yl)oxyethyl]phenylamino-2-methylthiopyrimidine as a yellow oil. Mass spectrum (ESI) MH^+ = 529, 531.

c) A solution of 2.6 g (4.9 mmol) of 5-(2-bromoanilino)methyl-4-[3-(2-(tetrahydropyran-2-yl)oxyethyl]phenylamino-2-methylthiopyrimidine in 60 ml of tetrahydrofuran was treated with 2 ml (14.4 mmol) of triethylamine and the mixture was added dropwise to a solution, cooled in ice, of 3ml of phosgene (20% in toluene) in 20 ml of tetrahydrofuran. After 1 hour 50 ml of saturated aqueous ammonium chloride were added. The organic phase was separated, dried over magnesium sulphate, filtered and evaporated. The residue was dissolved in 100 ml of methanol and 20 ml of saturated hydrochloric acid in ethyl acetate were added. After 10 minutes the mixture was evaporated to give 1.8 g (78%) of 3-(2-bromophenyl)-7-methylthio-3,4-dihydro-1-(3-(2-hydroxyethyl)phenyl)-pyrimido[4,5-d]pyrimidin-2(1H)-one as an off-white solid. Mass spectrum (ESI) MH^+ = 471, 473.

d) A solution of 1.4 g (3 mmol) of 3-(2-bromophenyl)-7-methylthio-3,4-dihydro-1-(3-(2-hydroxyethyl)phenyl)pyrimido[4,5-d]pyrimidin-2(1H)-one in 60 ml of dichloromethane was treated with 2 g (6 mmol) of 3-chloroperbenzoic acid (50% w/w water). After 18 hours 40 ml of saturated aqueous sodium bicarbonate solution were added. The organic phase was dried over magnesium sulphate, filtered and evaporated to give 1.45 g (100%) of 3-(2-bromophenyl)-7-methanesulphonyl-3,4-dihydro-1-[3-(2-hydroxyethyl)-phenyl]pyrimido[4,5-d]pyrimidin-2(1H)-one as a white solid. Mass spectrum (ESI) MH^+ = 503, 505.

Claims:

1. Compounds of the general formula



(I)

wherein

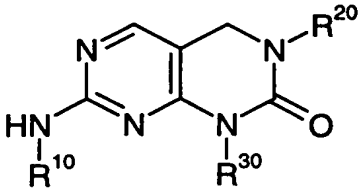
R^1 represents hydrogen, lower alkyl, aryl, aryl-lower alkyl, heteroaryl, heteroaryl-lower alkyl, lower cycloalkyl or lower cycloalkyl-lower alkyl,

R^2 represents lower alkyl, aryl, aryl-lower alkyl, heteroaryl, heteroaryl-lower alkyl, lower cycloalkyl or lower cycloalkyl-lower alkyl, and

R^3 represents hydrogen, lower alkyl, aryl, aryl-lower alkyl, heteroaryl, heteroaryl-lower alkyl, lower cycloalkyl, lower cycloalkenyl or lower cycloalkyl-lower alkyl,

and pharmaceutically acceptable salts of basic compounds of formula I with acids.

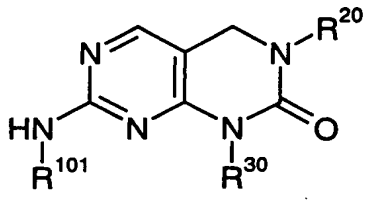
2. Compounds according to claim 1 of the general formula



(Ia)

wherein R^{10} represents lower alkyl, aryl or aryl-lower alkyl, R^{20} represents aryl and R^{30} represents hydrogen, lower alkyl, aryl or aryl-lower alkyl.

3. Compounds according to claim 2 of the general formula



(Iai)

wherein R^{101} represents aryl and R^{20} and R^{30} have the significance given in claim 2.

4. Compounds according to claim 3, wherein R^{101} represents phenyl.

5. Compounds according to claim 4, wherein R^{20} represents halophenyl.

6. Compounds according to claim 4, wherein R^{20} represents 2,6-dichlorophenyl.

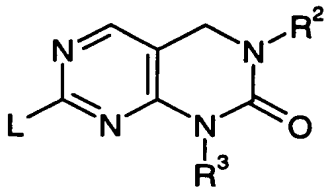
7. Compounds according to any one of claims 2 to 6, wherein R^{30} represents phenyl substituted by a group of the formula -Z-NR^4R^5 in which Z represents a spacer group and R^4 and R^5 each individually represent hydrogen or lower alkyl or R^4 and R^5 together with the nitrogen atom to which they are attached represent a 4-, 5- or 6-membered saturated or partially unsaturated or 5- or 6-membered aromatic heterocyclic group which contains one or more hetero atoms selected from nitrogen, sulphur and oxygen and which is optionally substituted by lower alkyl, lower alkoxy and/or oxo and/or which is optionally benz-fused.

8. 1-[3-(2-Aminoethyl)phenyl]-7-anilino-3-(2,6-dichlorophenyl)-3,4-dihydro-pyrimido[4,5-d]pyrimidin-2(1H)-one.

9. Compounds according to any one of claims 1 to 8 for use as medicaments, especially in the treatment or prophylaxis of inflammatory, immunological, oncological, bronchopulmonary, dermatological and cardiovascular disorders, in the treatment of asthma, central nervous system disorders or diabetic complications or for the prevention of graft rejection following transplant surgery.

10. A process for the manufacture of the compounds according to any one of claims 1 to 8, which process comprises

(a) reacting a compound of the general formula



(II)

wherein R^2 and R^3 have the significance given in claim 1, with the proviso that any hydroxy or amino group present may be in protected form, and L signifies lower alkylthio or lower alkanesulphonyl,

with an amine of the general formula

$$R^1—NH_2 \qquad \text{(III)}$$

wherein R^1 has the significance given in claim 1, with the proviso that any hydroxy or amino group present may be in protected form,

and, where required, converting a protected hydroxy or protected amino group present in the reaction product into a free hydroxy or free amino group,

or

b) for the manufacture of a compound of formula I in which R^1 represents hydrogen, cleaving off the aryl-methyl group from a compound of formula I in which R^1 signifies aryl-methyl,

and

c) if desired, converting a basic compound of formula I obtained into a pharmaceutically acceptable salt with an acid.

11. Compounds of formula II given in claim 10.

12. A pharmaceutical preparation, especially a pharmaceutical preparation for the treatment or prophylaxis of inflammatory, immunological, oncological, broncho-pulmonary, dermatological and cardiovascular disorders, for the treatment of asthma, central nervous system disorders or diabetic complications or for the prevention of graft rejection following transplant surgery, containing a compound according to any one of claims 1 to 8 in association with a compatible pharmaceutical carrier material.

13. A process for the production of a pharmaceutical preparation, especially a pharmaceutical preparation for the treatment or prophylaxis of inflammatory, immuno-logical, oncological, bronchopulmonary, dermatological and cardiovascular disorders, for

the treatment of asthma, central nervous system disorders or diabetic complications or for the prevention of graft rejection following transplant surgery, which process comprises bringing one or more compounds according to any one of claims 1 to 8 and, if desired, one or more other therapeutically valuable substances into a galenical administration form together with a compatible pharmaceutical carrier.

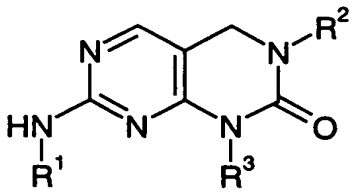
14. The use of a compound according to any one of claims 1 to 8 in the treatment or prophylaxis of illnesses, especially in the treatment or prophylaxis of inflammatory, immunological, oncological, bronchopulmonary, dermatological and cardiovascular disorders, for the treatment of asthma, central nervous system disorders or diabetic complications or for the prevention of graft rejection following transplant surgery.

15. Compounds according to any one of claims 1 to 8 and their pharmaceutically acceptable salts, when manufactured according to the process claimed in claim 10 or according to a process equivalent thereto.

16. The invention as hereinbefore described.

Abstract

Amino-substituted dihydropyrimido[4,5-d]pyrimidinones of the formula



(I)

in which R^1 represents hydrogen, lower alkyl, aryl, aryl-lower alkyl, heteroaryl, heteroaryl-lower alkyl, lower cycloalkyl or lower cycloalkyl-lower alkyl, R^2 represents lower alkyl, aryl, aryl-lower alkyl, heteroaryl, heteroaryl-lower alkyl, lower cycloalkyl or lower cycloalkyl-lower alkyl, and R^3 represents hydrogen, lower alkyl, aryl, aryl-lower alkyl, heteroaryl, heteroaryl-lower alkyl, lower cycloalkyl, lower cycloalkenyl or lower cycloalkyl-lower alkyl, and pharmaceutically acceptable salts of basic compounds of formula I with acids are protein kinase inhibitors. They can be used in the treatment or prophylaxis of inflammatory, immunological, oncological, bronchopulmonary, dermatological and cardiovascular disorders, in the treatment of asthma, central nervous system disorders or diabetic complications or for the prevention of graft rejection following transplant surgery.

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HOFFMANN-LA ROCHE INC.
340 KINGSLAND STREET
NUTLEY, NEW JERSEY 07110